Original Communications

THE PASSAGE OF SPERMS AND EGGS THROUGH THE OVIDUCTS OF THE RABBIT AND OF THE HUMAN BEING WITH A CONSIDERATION OF SAMPSON'S THEORY OF HEMORRHAGIC OR CHOCOLATE CYSTS

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1. INTRODUCTION

THE passage of sperms and eggs through the oviducts of mammals and especially of human beings has been a matter of long-standing controversy and has raised the general question of how materials are transported through these ducts. For several years past I have been working on this question with special reference to the rabbit, and I have discovered conditions in this mammal that have important bearings on sperm and egg transportation in the human being. An extended paper dealing with this problem in the higher vertebrates is in process of publication in the Philosophical Transactions of the Royal Society of London and the present contribution is a brief statement of that part of the longer paper which deals with human beings and other mammals. For additional information on the general topic the reader is referred to the longer paper.

2. ASCENT OF SPERMS

In copulation the male rabbit deposits the sperms at the inmost end of the vagina. The rabbit uterus is bipartite and under normal conditions the sperms make their way from the vagina into each uterus in a very short time. Living sperms have been identified in the lower end of the rabbit uterus one minute and fifty seconds after copulation. The maximum distance through which these sperms had passed up the uterus was thirteen millimeters. As rabbit sperms swim about 0.05 of a millimeter a second, it would have required them over four minutes to have

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covered this distance under their own locomotion and this computation is on the assumption that the sperms swam continuously straight ahead. The only explanation of their arrival at this point in a minute and fifty seconds appears to be the muscular activity of the region concerned. This activity is the motor aspect of the female sexual orgasm and was long ago pointed out by Beck (1875) as the probable means in human beings of the transfer of sperms from the vagina to the uterus. In such small mammals as the rat, judging from the observations of Hartman and Ball (1930), this muscular action may carry sperms to the apex of the uterine horn in less than two minutes, a condition probably not to be found in the larger forms. It is also likely that in rabbits and in human beings sperms make their way from the vagina into the uterus through their own locomotion but this form of transfer, already described by Walton (1930) for the rabbit, is scarcely to be regarded as normal. At least, it does not appear to represent a step in which the female reproductive apparatus can be said to be functioning at full efficiency.

The uterus of the rabbit, like that of the woman, is very slightly ciliated. If living sperms are injected into the top of a fresh uterus from a rabbit, they will find their way to the bottom of this organ in about two hours. If they are injected into the bottom they will reach the top in about the same time. In this respect the tube appears to be unpolarized and their passage through it seems to depend entirely upon their own locomotion. This is consistent with the observations of Lim and Chao (1926, 1927), who, by surgical operation, reversed a segment of a rabbit uterus without, however, reducing pregnancy. What has been demonstrated for the uterus in the rabbit may well apply to that in woman.

In most mammals, including human beings, a narrow uterine tube leads from the deep end of the uterus by a somewhat circuitous course to the immediate vicinity of the ovary where it opens by an expanded infundibulum. This tube is completely ciliated in both human beings and the rabbit and the cilia beat uniformly toward the uterus. Some of the older investigators believed that the sperms were carried through this tube by antiperistalsis. In all my experiences with living rabbit tubes I have never noticed evidence of antiperistalsis. Modern students are almost universally of the opinion that the sperms swim through the tube against the ciliary current as fishes swim upstream against the current of water. This opinion was expressed by Lott as early as 1872 and by many later workers, especially Adolphi (1905, 1906). The experimental basis upon which it rests consists in observations on sperms contained in a very shallow layer of fluid between a cover-glass and glass slide. When a slight current is generated in such a fluid the sperms are seen swimming against it. This is due to the fact that their heads are somewhat sticky and adhere slightly to the glass with which they are in contact; as a result of the current they swing round on their heads as a weather vane

about its point of attachment; thus their tails come to point downstream and when they swim they move upstream as a result of their orientation. Their direction is thus the outcome of a preceding and somewhat mechanical orientation. It was this evidence that led investigators to accept the view that sperms swim against the current in the oviducts; that is, that they are rheotactic. But sperms in the oviducts of mammals, including human beings, are not in contact with such surfaces as those used in the experiment just described. They are in the majority of cases suspended in fluid and only rarely in contact with the sides of the duct. If a preparation of the wall of the duct is made in fluid rich in living sperms and the whole is inspected under a microscope, the sperms will be seen to be swept with great velocity in the direction of the ciliary cur-
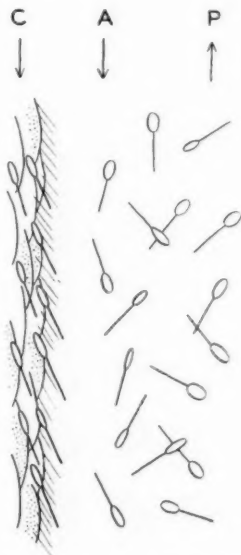

Fig. 1.—Free-hand sketch of the edge of a fold from the uterine tube of a rabbit showing the distribution of living sperms on the fold and in the adjacent fluid. A, ciliary current toward the uterus; C, ciliated epithelium on uterine fold; P, counter-current away from the uterus.

rent (Fig. 1). Their own locomotion plays almost no part in their distribution, for they are rushed indiscriminately down the duct by the ciliary action. Those that touch the sides of the duct often adhere there and remain fixed at the point of attachment. The condition of this test reproduces much more accurately the state of sperms in the oviduct than does that with cover-glass and slide, and it leads to the conclusion that the swimming of sperms against the current or sperm rheotaxis is not a significant element in the transfer of these cells. In other words, sperm rheotaxis is probably in large part a laboratory artefact rather than an actual occurrence in the oviducts.

If sperms are carried down the uterine tubes by the ciliary currents, how do they ever reach the upper ovarian end where the eggs are known

to be fertilized? In the rabbit the passage of the sperms through the uterine tubes requires about two hours. How this transfer can be accomplished may be discovered from experimental procedure. A tube from a freshly killed rabbit may be suspended with its fat and other adjacent parts in warm Ringer's solution and kept locally alive for some hours. If now a small amount of India ink in Ringer's solution is injected into the cavity of such a tube midway its length and the preparation is allowed to stand for an hour or more, the ink will be found to have approached both ends of the tube or even escaped from them. Ink discharged into the tube near its uterine end eventually makes it way out at the infundibulum and, similarly, ink injected into the infundibulum finally escapes into the uterus. These experimental results show conclusively that the tube is so constructed that materials like ink may pass either way throughout its length. If a freshly prepared tube is watched closely from the outside, no evidence of peristalsis or antiperistalsis will be seen. The muscular movements of the tube are slight and almost exactly like those of segmentation as seen in the vertebrate intestine; the tube constricts at one point and then relaxes, during which time a new constriction is established above and below the old one. These movements are not direct means of transporting materials through the tube; they serve merely to open and close it locally.

If the structure of the interior of the tube is now considered in relation to these movements, an obvious means of transporting the sperms will be seen. The uterine tube in the rabbit and in the human being is not a simple open duct but, as is well known, its cavity is partly divided by numerous folds which project from its outer wall irregularly into its interior (Fig. 3). The faces of these folds and the inner face of the wall of the tube are richly ciliated and all the cilia, as already noted, beat toward the uterus. When muscular constrictions occur at intervals along the length of the tube, as insegmentation, the spaces between the folds and any two such constrictions are temporarily cut off from communication with the corresponding spaces above and below. These spaces are in the form of elongated compartments with ciliated walls. Each compartment is filled with fluid and that portion of the fluid which is next the walls of the cavity moves under ciliary action downward toward the uterus. When it reaches the lower end of the compartment, since it is unable to escape because of the constriction, it turns and passes up the center of the compartment to the top whence it returns again over the side walls to repeat its course. In this way each compartment exhibits within itself a circulation which will carry sperms not only downward but also upward and thus in a very short time distribute them throughout the whole length of the compartment (Fig. 2). In transverse section (Fig. 3) such a compartment would exhibit a layer of fluid next its wall and moving downward and a column of fluid in its axis and moving upward. The two moving masses of fluid would be

separated by a thin layer of dead water. When a set of constrictions vanishes by relaxation and new sets appear at new points on the length of the tube, the region of the old compartments is divided in such a way that some of the contents form parts of new lower compartments and some of new upper compartments. Sperms that find themselves in the new upper compartments are thus advanced toward the ovary, while those below are turned back. By this process of continued dissolution
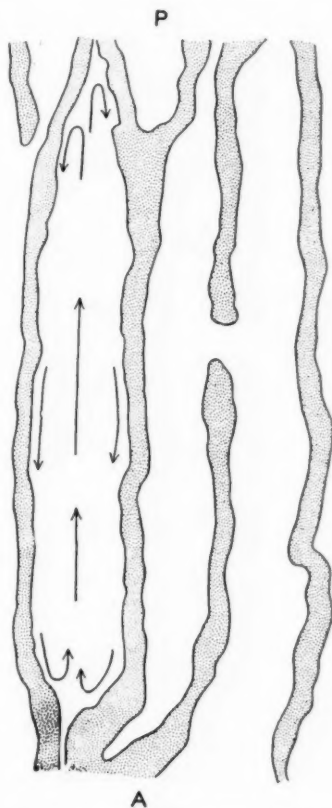

Fig. 2.—Diagram of a longitudinal section from the uterine tube of a rabbit. Three compartments are shown, in one of which the circulation is indicated by arrows; the currents toward the uterus are next the ciliated walls and the opposing current is in the axis of the compartment. A, toward the uterus; P, away from the uterus.

and formation of compartments sperms may gradually be transferred from one end of the duct to the other. The process, somewhat haphazard in nature, necessarily reduces the number of sperms as the tube is ascended. Nevertheless, the operation is one which in the end will transfer the sperms throughout the length of the duct. It is by this means that sperms and any other small particles, such as ink grains, are transported either up or down the tube. The operation is in no wise dependent upon the motility of the particles. Immobile granules of ink are transported as freely as swimming sperms. The length of the uterine

tube in the rabbit, about eight centimeters, is known to be ascended by sperms in approximately two hours. This time is also, roughly, the period required for the passage of ink through the tube. Hence, the time relations here are appropriate for the type of transportation assumed. This compartment system therefore affords an effective means for the last step in the transportation of sperms whereby they reach the region of the infundibulum where fertilization takes place.

The conditions observed in rabbits justify the opinion that in other mammals, including human beings, sperms are transferred from the vagina to the uterus usually through the muscular activities of the parts concerned and less usually by the locomotion of the sperms themselves. The sperms pass through the uterus under their own locomotion. The passage through the uterine tubes is not a result of sperm rheotaxis but is dependent upon the compartment system characteristic of these ducts.

3. THE DESCENT OF THE EGGS

The rabbit is remarkable in that its eggs are shed from the ovary approximately ten hours after intercourse with the male. In this respect it is unlike most mammals in which, as is well known, the eggs are discharged in relation to the physiologic rhythm of the female. Shortly after the eggs leave the ovary of the rabbit they accumulate in the infundibulum and then make their way in the course of three to four days through the length of the uterine tube. As the eggs are devoid of means of locomotion, they must pass through the tube as a result of the activity of its walls. These are muscular and ciliated. Some authors have maintained that the effective elements in this transfer are ciliary, others that they are muscular, and still others that both elements are concerned with transportation. About a decade and a half ago a somewhat heated discussion on this subject took place between Sobotta and Grosser. Grosser (1915, 1918) maintained that the tubal cilia were the exclusive means of transporting the eggs. This opinion was opposed by Sobotta (1914, 1915, 1916) who declared in favor of muscular action. Sobotta pointed out that cilia were absent from the lower part of the tubes in mice and rats and that consequently in such a region the only means of transportation was muscular. This view has now been rather generally accepted.

Though it must be admitted that under certain conditions muscles are the only means of transportation for the egg, it does not follow that cilia may not also at times have a part in this operation. It has been maintained by some workers, such as Heil (1893), Hofmeier (1893), and von Mikulicz-Radecki (1926), that the tubal cilia are too weak to move the mammal egg. But it is doubtful whether the evidence adduced by these workers is conclusive. They have attempted to test this question by placing the eggs on the ciliated surfaces of open tubes. Such a condition is very unfavorable as a test of the mechanical efficiency of cilia. They are thus placed in a position where they are least effective. In a closed

tube they can act upon objects the size of the egg much more successfully. The rabbit egg is a sphere with a diameter of approximately 0.12 mm. When an egg of this size is compared with the actual spaces in the uterine tube (Fig. 3), it will be seen that the egg is of such a size that in all cases it would press against the ciliated walls. Such a condition is most favorable for the ciliary transportation of a body like the egg, and since it is known not only that rabbit eggs will pass through the tubes normally, but that similarly sized eggs of nematodes (Lode, 1894) will, under experimental conditions, also make the passage of the tubes, it seems likely, considering the sizes of these objects in relation to the ciliated spaces in the tube, that cilia play a not inconsiderable part in this transfer.

The special transporting actions of the uterine tubes are determined, as the preceding discussion shows, by the size of the bodies concerned. Small particles, such as ink granules or sperms, are transported either
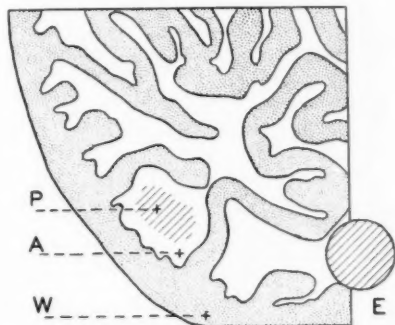
Fig. 3.—Diagram of a quadrant of a transverse section from the uterine tube of a rabbit. A, ciliary current on the periphery of a compartment and toward the uterus; E, outline of egg drawn to the same scale as that of the tube; P, counter-current in the middle of a compartment and away from the uterus; W, wall of the uterine tube.

up or down the tubes. Large particles of the size of the mammalian egg are carried down the tubes only. This difference seems to be characteristic of these bodies and depends upon their relative sizes, and the statement embodying this view may be set down as the law of the tube. Certainly the structural organization of the tube as well as the experimental evidence brought forward favor this interpretation and make clear the remarkable property of the tube; namely, the capacity to transport objects of appropriate size toward the ovary or away from the ovary even at the same moment.

4. SAMPSON'S THEORY OF HEMORRHAGIC OR CHOCOLATE CYSTS

It is well known that the region of the ovary in mature women may be the seat of the formation of cysts of a brownish color and of an unusual character. These cysts exhibit menstrual activities corresponding in time and general character with the menstruation of the person concerned. The blood discharged into their cavities is retained there, be-

comes brown in color, and thus gives to the cyst the special characters from which it gets its name. One of the remarkable features of the cyst is that it is lined with an epithelium most strikingly like that of the human uterus. In consequence of these peculiarities Sampson (1921, 1922) was led to advance the hypothesis that the cysts are growths from live epithelial cells liberated at menstruation from the inner face of the uterus and transported by some means unknown through the uterine tubes to be discharged in the vicinity of the ovary. This view of the formation of chocolate cysts has been supported by more or less experimental evidence (Jacobson, 1922), but it has never been made clear how immotile epithelial cells could make their way from the uterus to the ovary against the ciliary current of the tube. If, however, the compartment hypothesis described in this paper is a true statement of the way in which the tubes act, then this hypothesis offers a satisfactory explanation of the method by which freed epithelial cells from the uterus could be transported to the neighborhood of the ovary, for, since such cells are relatively small, they could be carried by the currents of the compartment system, as the sperms are, to the region of the ovary where they could attach themselves and grow as a transplant into a cyst. In this way the compartment hypothesis of the action of the uterine tubes affords not only an explanation of the transportation of sperms but also of that of the cells from which hemorrhagic or chocolate cysts may grow.

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MATERNAL MORTALITY AND THE MERCUROCHROME TECHNIC

An Analysis of the Deaths Following 15,647 Deliveries at the Methodist Episcopal Hospital, Brooklyn, N. Y., 10,000 of Which Followed the Use of Mercurochrome as a Vaginal Antiseptic

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IN THE United States registration area for 1929, the maternal death rate was 7 per 1,000 live births. Of this 42.8 per cent was due to puerperal sepsis.

For the five cities having a population of over 1,000,000 the percentage of maternal deaths due to puerperal septicemia is as follows: New York 34.6, Philadelphia 37.8, Chicago 41.5, Detroit 49.3, and Los Angeles 51.6. Ronsheim in a review of the mortality at the Jewish Hospital in Brooklyn, showed that 40 per cent of their maternal deaths was due to sepsis.

Thus, puerperal sepsis accounts for from 34 to 50 per cent of all maternal deaths. This percentage may be far too low when we consider that there is undoubtedly some inaccuracy in these reports, due to the fact that many patients who have puerperal sepsis with a toxemia or terminal pneumonia could easily be classified by the attending physician as dying from these conditions, while the cause of death was puerperal sepsis. Then again, when there is any doubt in the mind of the attending physician as to the presence of puerperal sepsis, he will often sign the death certificate giving some other reason for the actual cause of death.

TABLE I.   MATERNAL DEATHS, METHODIST EPISCOPAL HOSPITAL

	1919-1924	1925-1927	1928-1930	TOTAL
Total deliveries	5115	5253	5279	15647
Total deaths	54	32	22	108
Cesarean sections	265	177	177	619
Cesarean section deaths	19	4	5	28
Deliveries less cesarean sections	4974	5076	5102	15154
Deaths less cesarean sections	35	28	17	80
Viable vaginal delivery deaths	28	17	7	52
Died undelivered or delivered before admission	4	6	2	12
Premature deaths				
From 3 to 7 months	3	3	7	13
Under 3 months	0	2	1	3
Died within 24 hours	16	9	4	29

In the following report, I have endeavored to analyze the maternal deaths following 15,647 deliveries at the Methodist Episcopal Hospital, the deaths from puerperal sepsis having been analyzed in detail.

From 1919 to 1924 inclusive, as is shown in Table I, before the use of mercurochrome, there were 5115 cases with 54 maternal deaths. Nineteen of these followed cesarean sections, leaving 35 deaths from vaginal deliveries and of these, 28 were in patients over 7 months pregnant. This may be compared with 5253 deliveries during the development stage
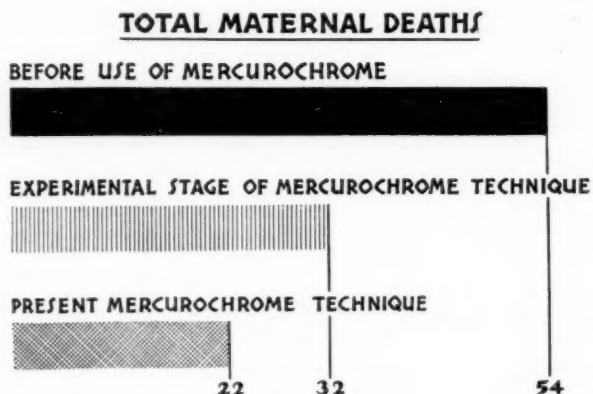
TOTAL MATERNAL DEATHS

BEFORE USE OF MERCUROCHROME

EXPERIMENTAL STAGE OF MERCUROCHROME TECHNIQUE

PRESENT MERCUROCHROME TECHNIQUE

22   32   54

Fig. 1.

of the mercurochrome technic when there were 32 maternal deaths, 4 of which followed cesarean sections and 17 followed the vaginal delivery of a viable child. With the latest mercurochrome technic there were 5279 deliveries with only 22 maternal deaths, 5 of these following cesarean sections and 7 following viable vaginal deliveries.

MATERNAL DEATHS
FOLLOWING VIABLE VAGINAL DELIVERIES

WITHOUT MERCUROCHROME

EXPERIMENTAL STAGE

PRESENT TECHNIQUE
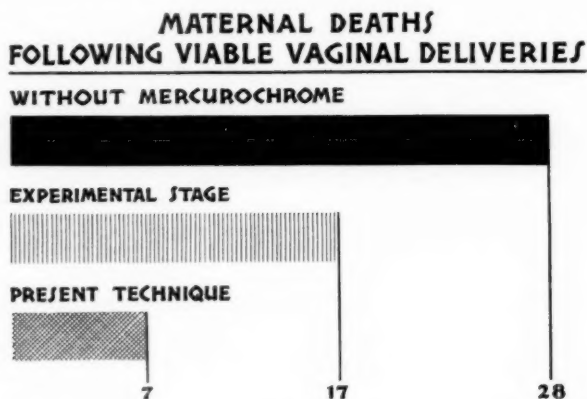
7   17   28

Fig. 2.

A comparison of these three periods is very striking and the marked decrease in the maternal deaths can be attributed partly to the fact that we have discarded the use of cesarean section in eclampsia, partly perhaps to the fact that we do better obstetrics, but the most striking factor is the reduction in the deaths from puerperal sepsis. Thus, from Table II it will be seen that there were 16 deaths from sepsis in the first period, 10 in the second, and only 3 in the last; one a full-term normal delivery,

one a cesarean section, and the third a five and one-half months' miscarriage.

There were 10 deaths from shock and hemorrhage before the use of mercurochrome, 3 during the experimental stage, and only 3 during the last 5,000 deliveries. Eclampsia and toxemia accounted for 14 in the first series, 3 in the second, and 4 in the last. Patients with toxemia and eclampsia have a lowered resistance following delivery, and they are very susceptible to infection. This is borne out by the fact that during the

TABLE II. CAUSE OF DEATH

	1919-24	1925-27	1928-30	TOTAL
Viable Vaginal Deliveries—51				
Sepsis	6	8	1	15
Shock and hemorrhage	8	2	2	12
Cardiac	2	1	0	3
Acute yellow atrophy of liver	1	0	0	1
Appendicitis	0	1	0	1
Eclampsia	3	0	0	3
Embolism	1	1	2	4
Inverted uterus	0	2	0	2
Placenta previa	1	1	0	2
Pneumonia	2	1	1	4
Psychosis	0	0	1	1
Pulmonary tuberculosis	1	0	0	1
Ruptured uterus	1	0	0	1
Toxemia	1	0	0	1
Cesarean Section Deaths—27				
Sepsis	7	1	1	9
Shock and hemorrhage	2	0	0	2
Cardiac	2	1	2	5
Cerebral hemorrhage	0	0	1	1
Eclampsia	4	1	0	5
Embolism	0	1	0	1
Thrombophlebitis	0	0	1	1
Toxemia	3	0	0	3
Delivered Before Admission and Not Delivered—12				
Sepsis	1	0	0	1
Shock and hemorrhage	0	1	0	1
Cardiac	0	1	0	1
Acute yellow atrophy of liver	0	1	0	1
Eclampsia	3	2	1	6
Hyperemesis gravidarum	0	0	1	1
Salvarsan (?)	0	1	0	1
Under Three Months—3				
Encephalitis	0	1	0	1
Hyperemesis gravidarum	0	1	1	2
Between Three and Seven Months—14				
Sepsis	2	0	1	3
Shock and hemorrhage	0	0	1	1
Cardiac	1	1	0	2
Acute yellow atrophy of liver	0	1	0	1
Eclampsia	0	0	1	1
Embolism	0	0	1	1
Hyperemesis gravidarum	1	0	0	1
Placenta previa	0	1	0	1
Pyelitis	0	0	1	1
Toxemia	0	0	2	2

period from 1919 to 1924, inclusive, there were 4 additional deaths from
puerperal sepsis in which there was either a toxemia or an eclampsia,
making a total of 18 deaths in which this condition played a part. While
following the use of mercurochrome, toxemia and eclampsia were not a
contributing factor in the septic deaths.

MATERNAL DEATHS FROM PUERPERAL SEPSIS

On the Obstetrical Service of the Methodist Episcopal Hospital, there
were 108 maternal deaths during the last eleven years, 29 of which were
due to puerperal sepsis; 4 of these patients were either not delivered or
delivered before the period of viability. This leaves a death rate from
puerperal sepsis of 22 per cent, while during the last three years there
has been but one death from sepsis following the vaginal delivery of
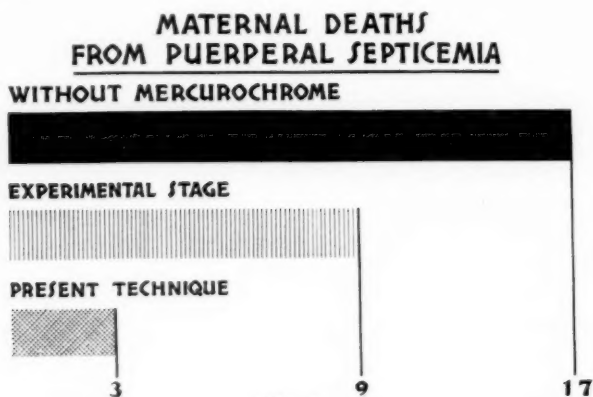a viable child.

MATERNAL DEATHS
FROM PUERPERAL SEPTICEMIA

WITHOUT MERCUROCHROME

EXPERIMENTAL STAGE

PRESENT TECHNIQUE

3   9   17

Fig. 3.

A. BEFORE THE USE OF MERCUROCHROME

An analysis of the deaths from infection before the use of mercuro-
chrome, shows that 6 deaths followed the vaginal delivery of a viable
child. All these patients were multiparae, ranging in age from twenty-
seven to forty-one, with an average morbidity of seventeen days each.
Only 3 had vaginal examinations, but 5 of the 6 had a period of dry
labor averaging twenty-two hours each. This was undoubtedly one
of the most important factors in the development of the sepsis. If
the majority of the bacteria had been killed in the vagina at the
onset of labor and by the use of regular instillations, so that the entrance
of extraneous infection could be avoided, I believe nearly all of these
women could have been saved. The average duration of labor was
thirteen hours. The upper part of the vagina may be sterile at
the onset of labor, but the advance and regression of the presenting
part, undoubtedly plays some part in bringing the bacteria from the
introitus and lower vagina up to the cervix and into the uterine
cavity, as demonstrated by Bessessen and Bessessen. Three of the
deliveries were operative. In 2 patients, the temperature developed

on the day of delivery and 1 each on the third, fourth, fifth, and eighth day. The blood cultures were positive in 3, negative in 2, and in 1 it was not taken. The average life of the patient following delivery was 12 days.

Without the use of mercurochrome there were 7 septic deaths in 265 cesarean sections, or one in 37.8. The average age of the patients was 34.9 years. Five were primiparae, 2 multiparae. Two had no examinations, 3 only rectal, and 2 vaginal and rectal examinations. The membranes were unruptured in 4. The average morbidity was 12.2 days. The onset of the temperature was on the day of operation in all but one. Six of the cesarean sections were primary and 1 was secondary. The average life of the patient following operation was 12.5 days. The hemoglobin averaged 57.4 per cent; the red cells for 5 cases, 3,200,000, and the leucocytes in 6 cases were 15,000, with an average of 89 per cent poly-

CESAREAN DEATHS FROM SEPSIS

WITHOUT MERCUROCHROME

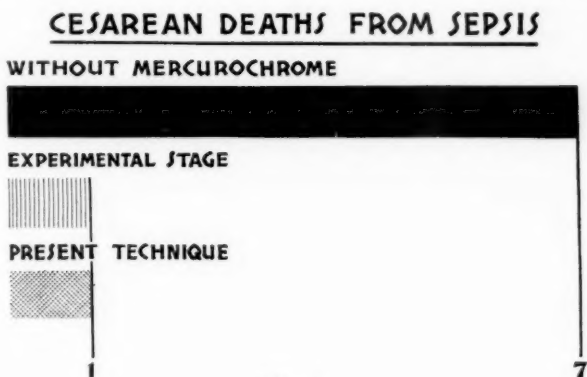EXPERIMENTAL STAGE

PRESENT TECHNIQUE

Fig. 4.

morphonuclears. The blood cultures were not taken in 3, were negative in 3, and in 1 a streptococcus was recovered. Postpartum infection was the factor that determined the deaths of this series of cases. There were other contributing factors; such as, eclampsia, toxemia, and anemia, but had the resistance of the patients not been lowered by these conditions, they might have been able to take care of the infection.

In the miscellaneous group there were 3 cases; one a premature labor which was induced for toxemia, 8 minims of pituitrin given during labor, and the autopsy showed a small perforation in the fundus of the uterus, which caused a peritonitis. Another was a five and one-half months' abdominal hysterotomy for a preeclamptic toxemia and chronic nephritis. The last of this series was a very interesting case diagnosed as varicella, the patient dying from a hemolytic streptococcus before delivery.

B. EXPERIMENTAL STAGE OF MERCUROCHROME

In this experimental mercurochrome group, there were 8 deaths from sepsis following viable vaginal deliveries. This includes 2 patients who did not die on the obstetric service. One was transferred to the surgical service because of the development of abscesses and the other, a suspected

typhoid, died on the medical service. The average age was 29.5 years. Three were primiparae, and 5 multiparae. Four were followed by rectal examinations only, 2 had vaginal, and 2 both rectal and vaginal examinations. The average duration of dry labor for 7 cases was 4.6 hours, while in 1 the membranes were ruptured several days before admission. The labor lasted for an average of 4.4 hours in 7, and in the other, 37 hours. The deliveries were spontaneous in 4, and in the rest, low or prophylactic forceps. One had no mercurochrome at all, another only at delivery, and the rest averaged 6.2 hours from instillation to delivery. One had fever before delivery, and the average day of onset for the rest was 2.2 days. The duration of illness averaged 15.5 days. The red cells averaged 3,500,000.

The large number of septic deaths in this period may be accounted for partly by the fact that our technic was faulty, but it is interesting to note that 1 patient did not have any mercurochrome, 1 only at delivery, another admitted with a temperature, was in labor for 37 hours and instilled only 2 hours before delivery. Then there were 4 deaths during the epidemic of puerperal sepsis in the spring of 1927. Of these patients 3 were multiparae, 3 had rectal examinations, and only 1 had a single vaginal examination. The labor averaged a little over 4 hours each and not one of the deliveries was operative. Hemolytic streptococcus was obtained from the blood of each one. The patients were removed to the isolation ward at the onset of symptoms, and although there were other patients there, no new cases developed in the isolation ward. The babies of these mothers were not affected. The patients were delivered on the following dates: January 12, February 25, March 15, and April 10. In no other cases did we recover the hemolytic streptococcus, and we feel that these were individual isolated cases and that contact was no factor. Although the delivery may have played some part in the development of the sepsis, we doubt if the infection entered by way of the vagina. Many other patients were delivered during this same period by forceps, version, induction by bag, and cesarean section, but not one of these developed a puerperal sepsis. Thus we felt that we were justified in keeping our wards open and considering these deaths as due to causes over which we had no control. We further believe that if we had not been using the mercurochrome preparation for delivery, we would have had instances of virulent sepsis in our operative cases as well, and would undoubtedly have had to close our wards as was done at the Sloane Maternity under similar circumstances.

During this period there were 177 cesarean sections with 1 death from sepsis. A rate of 1 in 177, as compared with 1 in 37.8 when no mercurochrome was used.

This patient died from sepsis in spite of the use of mercurochrome. She was a primipara with unruptured membranes, who went into shock during the anesthesia. She bled profusely during the operation and later developed a generalized

peritonitis. Dr. Beach, in commenting on this case before the New York Obstetrical Society, stated that "There was a possibility that the intestines had been punctured during the sewing up of the peritoneum. The patient took the anesthetic poorly and while sewing up the peritoneal cavity, she was coughing and protruding her intestines into the wound."

C. PRESENT MERCUROCHROME TECHNIC

In the last 5,000 cases occurring in the hospital, there was only 1 death due to sepsis following vaginal deliveries with viable babies. This patient was a para ii, thirty-six years old, who was instilled two hours before an easy spontaneous delivery. The membranes were ruptured at the time of delivery and she was in labor but nine hours. Autopsy showed that the infection spread from the placental site, that there was a thrombosis of the left ovarian and renal veins and a thrombus in the left ventricle. A staphylococcus was obtained from the blood stream.

There were 177 cesarean sections in this last period and again only one death that could be attributed to sepsis. This woman was a poor candidate for cesarean section. She was thirty-nine years old, a para iv; the membranes had been ruptured before admission and at least five days before the operation. She had been in labor for thirty-four hours and died from a peritonitis on the fourth day. The indication for cesarean section was an old trachelorrhaphy which interfered with the cervical dilatation. When the baby was delivered there was a definite sapremic odor and the uterus was undoubtedly infected before the time of the operation. If this uterus had been instilled with mercurochrome one hour before the operation, infection might have been avoided. There is a possibility that a low cesarean section or a hysterectomy may have saved this patient.

There was one other death from sepsis during this series, a para iii, thirty-three years old, who had chills and fever for two days before admission; had a five and one-half months' miscarriage, and the placenta showed evidence of infection as it was loaded with pus cells. An autopsy showed a pelvic thrombophlebitis.

SUMMARY

1. In a study of the maternal mortality following 15,647 deliveries, the cases are divided into three groups of approximately 5,000 each. The first group, when no vaginal antiseptic was used, covered a period from 1919 through 1924; the second, or experimental mercurochrome group, from 1925 through 1927; and the third group, with the latest mercurochrome technic, from 1928 to August, 1930.*

2. There were as many maternal deaths in the 5,000 deliveries before the use of mercurochrome as there were in the 10,000 following its use.

*From August 1, 1930, to January 1, 1932, there were 2695 deliveries with 3 maternal deaths, and 103 cesarean sections with 1 maternal death. Two of these were due to eclampsia; 2 were due to postpartum hemorrhage, 1 of which had a ruptured uterus. There has been 1 death from puerperal sepsis in 7797 vaginal deliveries.

3. Leaving out the cesarean sections, there were twice as many maternal deaths during the first 5,000 cases as there were during the last 5,000 cases, while with vaginal deliveries of viable children, there were four times as many in the first series.

4. The death rate from cesarean sections in the first group was 7.1 per cent and in the second and third groups, 2.6 per cent.

5. Shock and hemorrhage accounted for 8 deaths in the first series, 2 in the second and 2 in the third.

6. Eclampsia was given as the cause of 3 maternal deaths following the vaginal delivery of a viable child and 4 deaths following cesarean section in group one, while in the mercurochrome series, there was but one death from eclampsia in the vaginal deliveries of viable children.

7. In the first group there were 17 deaths from sepsis, 9 in the second, and 4 in the third.

Of the vaginal deliveries of viable children there were 6 deaths from puerperal sepsis in the first group, 8 in the second, and 1 in the third. Following cesarean section, there were 7 deaths from sepsis in the first group, 1 in the second, and 1 in the third.

8. In the last group but one of the deaths followed the vaginal delivery of a viable child. One followed cesarean section, and the third, a five and one-half months' miscarriage which was infected before admission.

CONCLUSIONS

If puerperal sepsis accounts for one-third to one-half of all maternal deaths, and is a preventable disease in which there has been no decrease during the last twenty-five years, does it not seem logical that the use of a vaginal antiseptic during labor and delivery might reduce the number of maternal deaths from this cause?

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494 FIRST STREET

THE AGE DISTRIBUTION OF 15,370 OBSTETRIC PATIENTS AND ITS EFFECT UPON THE TYPE OF DELIVERY

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IN RECENT years, a number of communications have appeared dealing with the obstetric risk rate as affected by the age of the patient. Most of these articles have concerned themselves chiefly with the so-called young or elderly primipara, and very few have attempted to present a cross section of the entire childbearing population. Therefore, it seemed of interest to investigate the age of a large series of women delivered in one community during a period of a number of years. There was approximately the same number of primiparae and multiparae in the group. Also the white and black races were about equally represented, thus making possible the investigation of age racial differences. Finally, a brief study was made concerning the influence of age on the type of delivery, with reference to race and parity.

It may be stated that less than 10 per cent of the cases in this series were private. The great majority were ward patients, and most of these of a social stratum so low that they were not able to pay the moderate ward fees. In other words, this series does not present a typical picture of society as a whole, but rather that of the crowded industrial districts of a large city.

For this investigation, we have taken a series of 15,370 consecutive deliveries on the obstetric service of the Johns Hopkins Hospital during a period of approximately 23 years (January 1, 1907, to December 31, 1929). Only such women as were delivered after the fetus had reached a period of viability (1500 gm.) have been considered.

The distribution of the patients according to race and parity is as follows:

TABLE I.

	WHITE		BLACK		TOTALS	
Primiparae	4058	(26.40%)	4348	(28.29%)	8406	(54.69%)
Multiparae	3747	(24.38%)	3217	(20.93%)	6964	(45.31%)
Totals	7805	(50.78%)	7565	(49.22%)	15,370	

Table I shows that the total number of whites and blacks very closely approximate one another. On the other hand, there is a wider difference between primiparae and multiparae, there being relatively more primiparae among the blacks than the whites; yet the total in each rubric seems sufficiently large to make our analyses of considerable significance.

Table II shows that the mean age for the entire group of patients is just under 24 years. There is a difference of 6.44 years between the average primipara and multipara. This difference is greater in the white race (6.88 years) than in the black (5.70 years). The mean age throughout is less in the black than in the white. The average black woman in Baltimore has her first baby at the age of 19.93 years, which is 1.97 years earlier than the white. An even greater difference (3.15 years) is observed between the multiparae. These variations may at

TABLE II. FREQUENCY DISTRIBUTION OF PATIENTS ACCORDING TO AGE, PARITY AND COLOR

| | AGE | | | | | | | UN- | | |
	-16	17-19	20-24	25-29	30-34	35-39	40-	KNOWN	TOTAL	MEAN AGE
White para 0	299	1347	1649	489	172	80	21	1	4058	21.89735±0.04905 years
White para x	5	202	1007	1037	797	491	199	9	3747	28.77740±0.06888 years
Black para 0	806	1976	1180	269	75	37	4	1	4348	19.92810±0.03668 years
Black para x	28	507	1244	737	373	242	85	1	3217	25.63120±0.07242 years
Both para 0	1105	3323	2829	758	247	117	25	2	8406	20.87875±0.03121 years
Both para x	33	709	2251	1774	1170	733	284	10	6964	27.32240±0.04675 years
Total white		304	1549	2656	1526	969	571	220	10	7805	25.19660±0.04933 years
Total black		834	2483	2424	1006	448	279	89	2	7565	22.30035±0.04200 years
Total pts.		1138	4032	5080	2532	1417	850	309	12	15,370	23.86150±0.03161 years

first glance seem rather small; but if they be tested by the division of the difference by its probable error, they may be shown to be statistically significant. Thus we find that with a difference of 1.97 years between the mean age of white and black primiparae, the probable error is 0.06 years, so that the difference is 32.12 times its probable error. Since any difference that is three or more times its probable error is usually considered significant, it is highly improbable that the above figure is due to chance. Similarly, applying the same test to the white and black multiparae the $\dfrac{\text{Diff.}}{\text{P.E.}}$ diff. = 31.50, and for total white and black patients equal 44.74. From the foregoing discussion, it seems evident that not only does the colored woman begin her childbearing career

TABLE III. INCIDENCE OF PATIENTS PER THOUSAND DELIVERIES ACCORDING TO AGE, PARITY, AND COLOR

	-16	17-19	20-24	AGE 25-29	30-34	35-39	40-
White para 0	74	332	406	121	42	20	5
Black para 0	185	455	271	62	17	9	1
White para x	1	54	270	278	213	131	53
Black para x	9	158	387	229	116	75	26
Total para 0	132	396	336	90	29	14	3
Total para x	5	102	324	255	168	105	41
Total white	39	199	341	196	124	73	28
Total black	110	328	321	133	59	37	12

at a definitely earlier age, but that there appears to be a shorter time interval between successive pregnancies. Tables III and IV offer further evidence in support of the points just adduced. Thus, practically two-thirds of the black women have their first delivery before they reach the age of 20; which is true of only two-fifths of the white. Furthermore, one-sixth of the blacks have become multiparae by this age, as contrasted with one-twentieth of the whites. On the other hand, only 2.7 per cent of the black primiparae are 30 years or more of age, while 6.7 per cent of the whites fall in this group, an incidence two and one-half times as great.

TABLE IV. PERCENTAGE DISTRIBUTION OF PATIENTS ACCORDING TO AGE, PARITY, AND COLOR

AGE	Black						White					
	PR.	%	M.	%	BOTH	%	PR.	%	M.	%	BOTH	%
Below 20	2782	64.0	535	16.6	3317	43.9	1646	40.6	207	5.5	1853	23.8
20 - 29	1449	33.3	1981	61.6	3430	45.4	2138	52.7	2044	54.7	4182	53.6
30 or over	116	2.7	700	21.8	816	10.8	273	6.7	1487	39.8	1760	22.6
Total	4347		3216		7563		4057		3738		7795	

	Both Races					
	PR.	%	M.	%	BOTH	%
Below 20	4428	52.7	742	10.7	5170	33.7
20 - 29	3587	42.7	4025	57.9	7612	49.6
30 or over	389	4.6	2187	31.4	2576	16.8
Total	8404		6954		15,358	

Again, it may be seen in Table III that out of a thousand white primiparae the rubric for maximum occurrence is age 20 to 24, as compared with the age 17 to 19 for the blacks. Considering as a young primipara a girl delivered before the age of 17, and as an elderly primipara a woman of 35 years or over, we arrive at the following figures, which again support the previous statements:

	WHITE	BLACK
Young primiparae	7.4%	18.5%
Elderly primiparae	2.5%	1.0%

Furthermore, our figures seem to indicate that the colored multipara finishes her childbearing career earlier than the white, since only 21.8 per cent of the former as against 39.8 per cent of the latter are over thirty years of age. Tables V and VI indicate that when the cases under discussion are subdivided according to type of delivery, still further racial differences become evident. The arbitrary division used here is full-term spontaneous, full-term operative, and premature (under 2500 gm., both spontaneous and operative). Despite the fact that the incidence of contracted pelvis is two and one-half times greater in the colored race, the percentage of operative deliveries in primiparae is less than among the whites. However, in multiparae the opposite is

TABLE V. PERCENTAGE DISTRIBUTION OF TYPES OF DELIVERY ACCORDING TO COLOR AND PARITY

	White				Black				Both Races			
	PARA 0		PARA X		PARA 0		PARA X		PARA 0		PARA X	
	CASES	%	CASES	%	CASES	%	CASES	%	CASES	%	CASES	%
F.T.S.	2943	72.5	2985	79.7	3345	76.9	2389	74.3	6288	74.8	5374	77.2
F.T.O.	936	23.1	570	15.2	693	15.9	535	16.6	1629	19.4	1105	15.9
Prem.	179	4.4	192	5.1	310	7.1	293	9.1	489	5.8	485	7.0
Total	4058		3747		4348		3217		8406		6964	

	PARA 0 AND PARA X				TOTAL PATIENTS	
	White		Black			
	CASES	%	CASES	%	CASES	%
F.T.S.	5928	75.95	5734	75.80	11,662	75.87
F.T.O.	1506	19.30	1228	16.23	2,734	17.79
Prem.	371	4.75	603	7.97	974	6.34
Total	7805		7565		15,370	

TABLE VI. FREQUENCY DISTRIBUTION OF TYPE OF DELIVERY ACCORDING TO AGE, PARITY, AND COLOR

	- 16				17 - 19				20 - 24				25 - 29			
	F.T.S.	F.T.O.	PREM.	TOTAL	F.T.S.	F.T.O.	PREM.	TOTAL	F.T.S.	F.T.O.	PREM.	TOTAL	F.T.S.	F.T.O.	PREM.	TOTAL
White para 0	236	49	14	299	1071	205	71	1347	1206	373	70	1649	303	171	15	489
Black para 0	623	122	61	806	1572	269	135	1976	903	194	83	1180	179	68	22	269
White para x	3	2	0	5	180	13	9	202	875	87	45	1007	828	166	43	1037
Black para x	20	3	5	28	389	70	48	507	981	169	94	1244	544	129	64	737
Total para 0	859	171	75	1105	2643	474	206	3323	2109	567	153	2829	482	239	37	758
Total para x	23	5	5	33	569	83	57	709	1856	256	139	2251	1372	295	107	1774
Total white	239	51	14	304	1251	218	80	1549	2081	460	115	2656	1131	337	58	1526
Total black	643	125	66	834	1961	339	183	2483	1884	363	177	2424	723	197	86	1006
Total Pts.	882	176	80	1138	3212	557	263	4032	3965	823	292	5080	1854	534	144	2532

TABLE VI. FREQUENCY DISTRIBUTION OF TYPE OF DELIVERY ACCORDING TO AGE, PARITY, AND COLOR (CONTINUED)

	30 - 34				35 - 39				40 -			
	F.T.S.	F.T.O.	PREM.	TOTAL	F.T.S.	F.T.O.	PREM.	TOTAL	F.T.S.	F.T.O.	PREM.	TOTAL
White para 0	92	77	3	172	28	46	6	80	6	15	0	21
Black para 0	42	25	8	75	22	14	1	37	3	1	0	4
White para x	626	129	42	797	340	118	33	491	129	52	18	199
Black para x	265	73	35	373	136	71	35	242	53	20	12	85
Total para 0	134	102	11	247	50	60	7	117	9	16	0	25
Total para x	891	202	77	1170	476	189	68	733	182	72	30	284
Total white	718	206	45	969	368	164	39	571	135	67	18	220
Total black	307	98	43	448	158	85	36	279	56	21	12	89
Total Pts.	1025	304	88	1417	526	249	75	850	191	88	30	309

true, though not to any marked extent. The lower average weight of the black infant and the increased malleability of its head may partially account for this fact. It will also be noted that the incidence of premature children is higher in the blacks, but in both races it occurs more commonly in the multiparous woman.
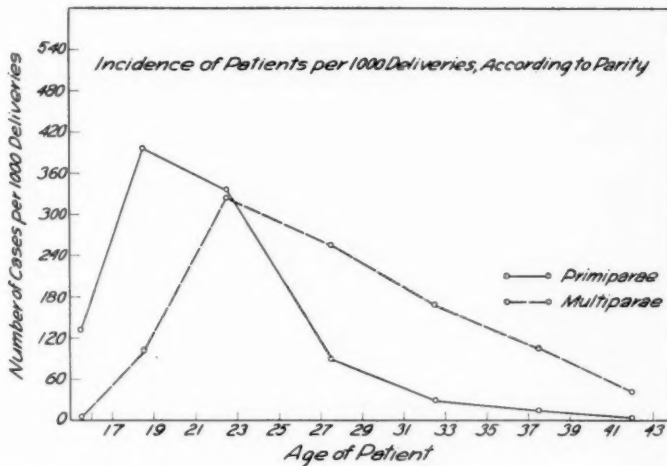

Fig. 1.—The age incidence of primiparae and multiparae of both races in terms of 1000 deliveries.
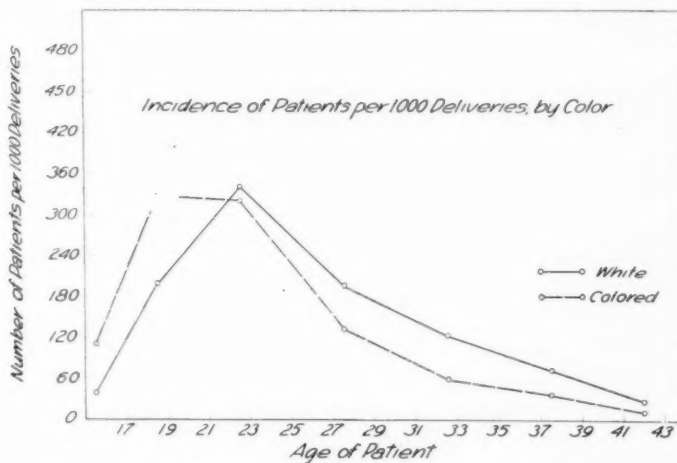

Fig. 2.—The age incidence according to race of combined primiparae and multiparae in terms of 1000 deliveries. Note that the black woman tends to begin and end her childbearing career earlier than the white.

There is a surprisingly high incidence of operative deliveries in the multiparae of both races. We consider our primiparous population as a fairly representative one, but the ratio of referred obstetric emergencies to normal cases among the multiparae is quite high and probably is the explanation of the above findings.

Figs. 1 to 6 indicate very clearly the influence of age on the type of delivery. For primiparae, the incidence of premature delivery seems little changed by age. However, in primiparae of both races beginning at an optimum between 17 and 19 years, the percentage of spontaneous
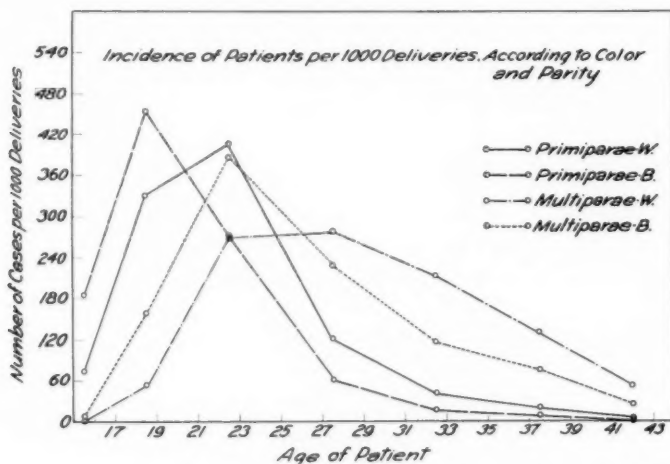
Fig. 3.—Showing age incidence in primiparae and multiparae of both races. Indicating that the greatest frequency of both first and subsequent labors occurs earlier in blacks than in whites, and that white women tend to bear more children in the later years of their reproductive career.
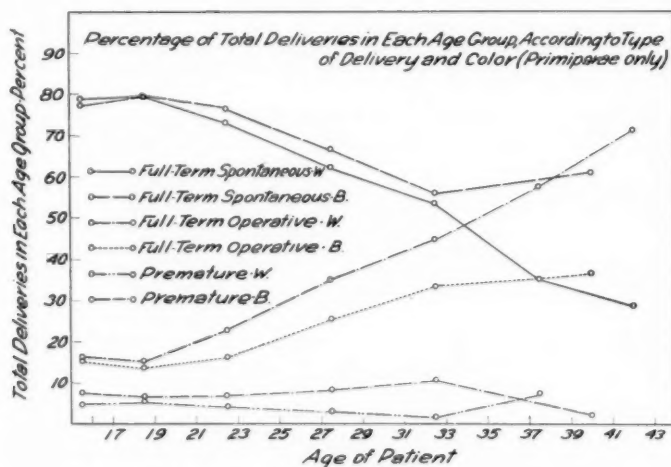
Fig. 4.—Showing the increased incidence of operative deliveries with advancing age in both races. Note that after the thirty-fourth year, there are more operative than spontaneous deliveries in white women.

deliveries begins to fall and is accompanied by a corresponding increase in the number of operative labors. In the white race a point is reached in the late thirties where there are more operative than spontaneous labors, whereas this does not obtain in the blacks. The same tendency, though not to such a marked extent, is observed among multiparae. In

the later age group the number of cases from which these percentages are obtained is in some instances so small as to make probable a considerable error of chance.   Nevertheless, it is believed that the general trend of the lines would hold for a larger series.   The practical appli-
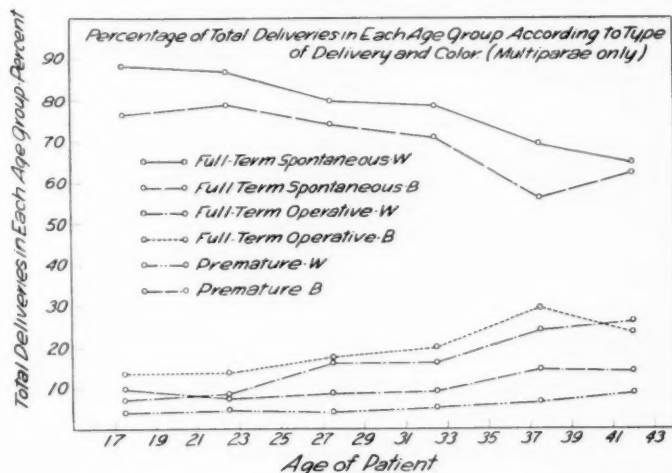

Fig. 5.—Showing that there are more spontaneous and fewer operative deliveries in white than in black multiparae at all ages. Note the greater incidence of premature deliveries in the black race.
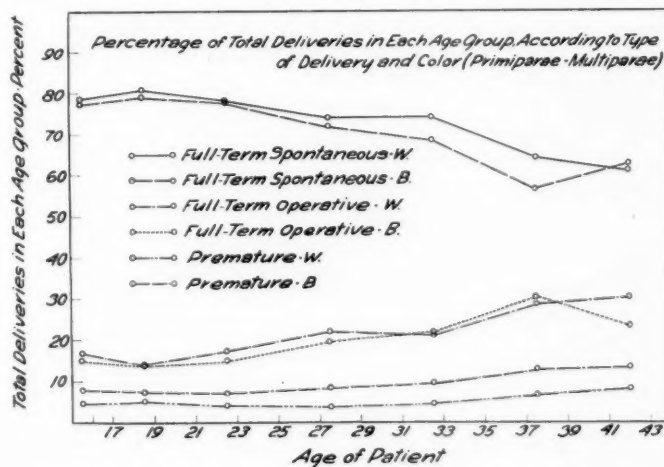

Fig. 6.—Represents the combination of Figs. 4 and 5, and shows that for all women of both races (primiparae and multiparae) the proportion of spontaneous to operative delivery is essentially the same

cation of these findings will be discussed more fully in a subsequent communication, when the correlation between type of delivery and fetal mortality will be shown.

Racial differences according to the influence of age on the type of delivery are not so marked. However, throughout there are more pre-

mature babies in the black women. The percentage of spontaneous terminations to labor does not fall as rapidly in the blacks, and the spontaneous and operative lines do not cross with increasing age as is observed among white women.

It is interesting that for both races the very young woman (under 17) has a slightly higher operative incidence than is found at the optimum point, which falls between 17 and 19 years.

CONCLUSIONS

1. The mean age of 15,370 obstetric patients, divided almost equally between the white and black races, and containing primiparae and multiparae in almost equal numbers, is just under 24 years. A difference of 6.44 years exists between primiparae and multiparae.

2. The mean age is significantly lower in black than in white primiparae (1.97 years); and an even greater variation was observed in the multiparae (3.15 years).

3. The number of "young primiparae" (under 17) is greater among the black race, while fewer "elderly primiparae" (35 or over) are found.

4. The childbearing career seems to end earlier in the black than in the white woman.

5. The ratio of operative to spontaneous deliveries at term is lower among black primiparae despite a much higher incidence of contracted pelvis. Likewise, a higher percentage of pregnancies terminating prematurely is observed in this race.

6. In both races, the percentage of operative deliveries increases with age and in the whites reaches a point in the late thirties where it exceeds the spontaneous type.

7. The probability of spontaneous termination of labor appears to be less good in very young women than in the age group of 17 to 19 years.

A NEW ANALYSIS OF DURATION OF PREGNANCY DATA

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THE duration of pregnancy problem, though more ancient than Hippocrates and still the constant source of a voluminous literature, has not as yet been studied by means of modern statistical methods. This is not surprising in view of the fact that the recent revolutionary discoveries in mathematical statistics relevant to the problem are still less generally understood than the theory of relativity, being almost entirely unknown outside of England and Russia, whereas research on duration of pregnancy in the last few years has principally centered in Germany.

The present study was undertaken in order to reanalyze by new methods the results of the older writers, and by gathering a new body of data for comparison, to contribute, if possible, some new light on this age-old subject.*

THE DATA

Our data were gathered from the histories of 2033 Stanford University obstetric clinic cases received at Lane Hospital, San Francisco, between September 1, 1926, and December 31, 1930. Three-fifths (1187 or 58 per cent) of the histories had to be discarded because of uncertainty in the beginning date of the last menstruation. (The rather loose term "duration of pregnancy" we define, as in America and Germany generally, to be the time from the beginning of the last menstruation until the day of delivery.) Forty-one other cases (2 per cent) were discarded because of stillbirths. Sixty-eight (3.3 per cent) were discarded because of a cesarean section delivery, and 73 (3.6 per cent) because father or mother was known to have a venereal disease. Any one of these three causes, we reasoned, indicated a pathologic condition or at least an abnormal condition which might disturb the mean for normal duration of pregnancy.

All cases were noted in which a living birth was recorded. (In California, as in many other states and countries, a living birth is recorded if the child, no matter how premature, has breathed.) The shortest duration in our data was 194 days; the longest, 317 days. In the end, 668 cases remained with which to work, including 537 of the white race, 70 Mexicans, 29 Negroes, 11 Japanese and Chinese, and 21 others (Filipinos, South Americans, and others of undefinable race.)

In the literature since 1850, moreover, were found the accompanying tables of data with enough detail to allow of comparison with our data:

TABLE I. PUBLISHED DATA ON DURATION OF PREGNANCY REANALYZED

AUTHOR	NO. OF CASES		DURATION IN DAYS	QUALIFICATIONS
	Duration calculated from last day of last menstruation:			
Reid[1]	500		251-316	
Périer[2]	1004		251-305	Duration longer than 305 days omitted
	Duration calculated from first day of last menstruation:			
Enge[3]	323		251-319	Wt. of child 4 kg. and over Gives also date of coitus in 142 cases
Stinnesbeck[4]	460		249-326	Wt. of child 3. to 3.5 kg.
Meyer[5]	2359	260 cases 2099 cases	180-250 250-330	Data read from his Fig. 7 Includes about 50% negroes
Schlichting[6]	402 excluding 14 stillbirths	1 case 1 case 400 cases	161 196 208-329	Gives wt. of child, age of mother, no. of previous pregnancies, and date of coitus
Ahlfeld[7]	155		247-322	Gives also date of coitus, counting the beginning date as the first instead of the zero day.

It will be noted that Meyer and Schlichting are the only ones of these authors to include in their detailed tables durations shorter than 247 days. On the other hand, all of them have included the very long durations except Périer who deliberately omitted durations longer than 305 days on the assumption that such durations indicated false recording of the beginning date.

We leave aside the tables of Périer, who excluded the very long durations, and those of Enge and Stinnesbeck, who limited their cases according to the weight of the child, obviously an unpredictable qualification. This leaves for comparison with our data the tables of Meyer, Schlichting, Ahlfeld, and Reid.

TESTS FOR HOMOGENEITY

It was first necessary to find out whether the cases listed in these four tables were sufficiently similar to our cases to allow of comparison. We therefore applied the χ^2 test for homogeneity to each of them separately with ours, and then, with a finer grouping, to the three tables which passed the first test and to our table simultaneously.[8]

To examine the consistency of the several statistical reports concerning duration of pregnancy, the χ^2 test was first applied to compare Meyer's data with ours, and then with Schlichting's. Meyer states that his cases include about 50 per cent Negroes, but he does not state whether or not stillbirths are included. This omission cannot, however, have

made much difference in the results, since stillbirths in Schlichting's table amount to 3 per cent of all cases, and in our data to 2 per cent of all cases. The inclusion in Table II of stillbirths in Schlichting's data and the exclusion of them in ours, since they were so few in number, we assumed would virtually offset any discrepancy due to the inclusion or exclusion of them in Meyer's data.

Table II presents the number of cases in the various classes according to length of pregnancy.

TABLE II. DURATIONS OF PREGNANCY FOUND IN THREE DIFFERENT INVESTIGATIONS

DURATION OF PREGNANCY	NUMBERS OF CASES FOUND BY		
	MEYER, BALTIMORE (BEFORE 1910) ABOUT 50% NEGROES NO. OF STILLBIRTHS NOT GIVEN	SCHLICHTING, MUNICH (1861-1879) INCLUDING 15 STILLBIRTHS	HOTELLING, SAN FRANCISCO (1926-1930) NOT INCLUDING 41 STILLBIRTHS INCLUDING 81.5% CAUCASIANS 4 % NEGROES 10 % MEXICANS 4.5% OTHERS
250-269 days	454	61	112
270-279 days	514	126	183
280-289 days	568	117	199
290 days and more	563	100	134
Totals	2099	404	628

The χ^2 test showed Meyer's data homogeneous neither with Schlichtings nor with ours. On the contrary, Schlichting's data appeared to be very homogeneous with ours, in spite of the fact that they were gathered so long ago and in a different country, and in spite of the fact that they included stillbirths while ours did not. For these reasons we were led to think that the 50 per cent Negroes in Meyer's data might have been the cause of the discrepancy between his cases and those of Schlichting and our own. It is more than likely that Schlichting had only white patients in his Munich clinic. Our cases included only 4 per cent Negroes, and were for the most part white. Meyer states[9] that he found the average pregnancy duration in the case of 1,186 Caucasians to be 279.8 days; in the case of 1,181 Negroes, 276.9 days, an approximate difference of 3 days.

TABLE III. DURATIONS OF PREGNANCY FOUND AT STANFORD UNIVERSITY CLINIC, CLASSIFIED BY RACE

DURATION OF PREGNANCY	CAUCASIANS	NEGROES	MEXICANS
250-269 days	79	8	22
270-279 days	145	10	13
280-289 days	165	7	16
290 days and more	113	3	14
Totals	502	28	65

On this account, we tried the χ^2 test upon our white patients as compared with our Negroes, and with our Mexicans, a mixture of Spanish and American Indian blood. The durations for the three races were classified as in Table III.

The χ^2 test showed that our guess had been correct and that the proportion of cases falling in each class differed materially in the three different races. The χ^2 test applied again to Schlichting's data and to ours when only white patients were included showed much less disproportionality than before, thus confirming our supposition that there must be racial differences in duration of pregnancy. Thereafter on this account we excluded all but the white patients from our cases for study.

Ahlfeld's data were also found to be very homogeneous with ours. It only remained to find out whether Reid's data were comparable with Schlichting's, Ahlfeld's, and ours. But Reid's durations dated from the last day of the last menstruation, whereas those of the other three bodies of data were reckoned from the first day of the last menstruation. We decided to allow 1, 3, 5, and 7 days, respectively, for the menstrual flow and add these periods to Reid's durations in order to compare them with those of the other investigators. A finer grouping was also made and the χ^2 test applied to all four tables at the same time.

Curiously enough, when 1 or 3 days were allowed for the menstrual flow, χ^2 was very small, giving evidence of great homogeneity, but when 5 days were allowed, it was very large, and when 7 days were

TABLE IV. TEST FOR HOMOGENEITY IN DURATIONS OF PREGNANCY FOUND IN FOUR DIFFERENT INVESTIGATIONS

(Allowing 3 days for menstrual hemorrhage)

DURATION OF PREGNANCY IN DAYS	NUMBER OF CASES FOUND BY				MARGINAL TOTALS	PROPORTIONS OF TOTALS
	REID	SCHLICHTING	AHLFELD	HOTELLING		
Reid: 251-260 Others: 254-263	29	31	5	23	88	0.0575
Reid: 261-270 Others: 264-273	82	63	32	89	266	0.1737
Reid: 271-280 Others: 274-283	172	132	56	180	540	0.3526
Reid: 281-290 Others: 284-293	146	99	38	149	432	0.2822
Reid: 291-316 Others: 294-319	71	57	17	60	205	0.1340
Totals	500	382	148	501	1531	1.0000

$\chi^2 = 12.306$.
n = 12
P = 0.44, giving evidence of great homogeneity.

allowed, it was still greater, showing that the average menstrual period among Reid's cases must have been not more than 4 nor less than 1 day. Here is a statistical indication substantiating current belief that the menstrual flow is normally not more than 3 days long.

Table IV classifies the durations when 3 days are allowed for the menstrual flow.

MEAN AND STANDARD DEVIATION OF NORMAL PREGNANCY

Having found four sets of records which, at least with the broad grouping used, are homogeneous, we are now ready to use them to find out what we can about the duration of pregnancy. We first seek to determine the average length of normal pregnancy, and the standard deviation from this average. For this purpose, we have grouped the durations of each column in Table IV in two-day intervals, putting in 0 whenever no cases occurred in a particular group. Since Reid's first recorded duration was in the two-day group, 251-252 days from the last day of the last menstruation, the durations for the other three homogeneous tables had to begin with durations of 254-255 days from the first day of the last menstruation, allowing three days for the average flow in Reid's cases. Similarly, since Reid's table ended with a duration of 315-316 days, the other tables had to end with durations of 318-319 days in order to make them all comparable with each other. This procedure excluded 1 case of Ahlfeld's (duration of 322 days); 5 cases of Schlichting's (durations of 322, 324, 324, 328, and 352 days respectively); but no cases from our data.

Our 537 cases, complete, grouped in two-day intervals, are given in Table V.

TABLE V. DURATIONS OF PREGNANCY AT LANE HOSPITAL, SAN FRANCISCO, 1926-30
(Caucasians only)
Grouped in two-day intervals

DURATIONS IN DAYS	NO. OF CASES	DURATIONS IN DAYS	NO. OF CASES	DURATIONS IN DAYS	NO. OF CASES
194-5	1	236-7	0	278-9	36
196-7	0	238-9	0	280-1	34
198-9	0	240-1	4	282-3	40
200-1	1	242-3	4	284-5	36
202-3	0	244-5	1	286-7	38
204-5	2	246-7	4	288-9	23
206-7	0	248-9	1	290-1	29
208-9	1	250-1	4	292-3	23
210-11	0	252-3	6	294-5	17
212-13	0	254-5	7	296-7	10
214-15	1	256-7	5	298-9	10
216-17	0	258-9	1	300-1	4
218-19	0	260-1	2	302-3	5
220-1	0	262-3	8	304-5	4
222-3	1	264-5	11	306-7	4
224-5	1	266-7	11	308-9	4
226-7	1	268-9	23	310-11	1
228-9	0	270-1	19	312-13	1
230-1	1	272-3	25	314-15	0
232-3	2	274-5	29	316-17	0
234-5	0	276-7	41	318-19	0

The mean and standard deviations of the four homogeneous sets of data are as found in Table VI.

TABLE VI. MEAN AND STANDARD DEVIATION OF NORMAL PREGNANCY DURATION
(254-319 days from first day of last menstruation)

	REID	SCHLICHTING	AHLFELD	HOTELLING
Mean Duration in days	281.7	282.8	280.7	281.4
Standard Deviation in days	±11.4	±12.4	±11.2	±10.7

The greatest difference between these means is between Schlichting's and Ahlfeld's, amounting to 2.1 days. To show that no significant differences exist among the four means, it is only necessary to test the difference between these two, the greatest and the least. The standard error of this difference is 1.1 days, and the difference between the longest and the shortest mean duration is therefore less than twice its standard error. Had the ratio been more than 2.5, the difference would have been deemed significant, but since it is less than 2.5, the means of these four groups of data cannot be considered significantly different from each other.

Our mean, it will be observed, of 281-283 days, for normal pregnancy, is slightly longer than that usually given, namely 280 days. Had we considered the duration of normal pregnancy to be at least 250 days from the first day of the last menstruation as most writers do, instead of 254 days as we did in order to be able to use Reid's data, our mean would no doubt have more nearly approached the usual figure.

The largest and the smallest dispersions about the mean, those found in Schlichting's and our own data, respectively, were found, contrary to the longest and shortest means, to have a very significant difference, although Reid's standard deviation of 11.4 days, and Ahlfeld's of 11.2 days were found to have no significant difference from ours of 10.8 days.

Undoubtedly, some factor was present in Schlichting's data to cause a wider dispersion about the mean than in the data of the other three tables. This may perhaps have been the fact that his cases were selected because the date of "fruchtbaren Cohabitation" was known, or it may have been that they were taken from a different racial or social class than those of the other three.

The standard deviation of 11 days, however, is longer than the standard deviation of 10 days found by Ellermann[10] after a study of the tables of four older writers, and of 8 days found by Hart[11] after a study of Reid's 500 cases. This difference of 1 to 3 days may be due to different methods of calculating the standard deviation or to differences in the data used on account of typographical or other errors.

Almost every writer on this subject speaks of mistakes he has found in the work of earlier authors. We came upon many such mistakes and carefully rechecked all the old tables as well as our own before using

them. In Ahlfeld's data, for instance, Lowenhardt, in subtracting one date from another, counted both end-days instead of only one; as this is contrary to accepted usage, we corrected all of his figures to make them correspond to the other data used. Frequent errors in subtraction were found in Schlichting's data; we assumed that the dates rather than the durations given were correct and recalculated all of the durations.

The fact that 11 days is the standard deviation from the mean of our own data as well as that of the rechecked data of two older writers leads us to believe that 11 days is more nearly correct than 10 or 8.

MEAN AND STANDARD DEVIATION OF COITUS-TO-BIRTH DURATIONS

Ahlfeld gives the date of coitus for his 155 cases as well as the date of the last menstruation. Siegel[12] and Nürnberger[13] have made more recent studies upon coitus-to-birth durations, although neither one seems to have published a detailed table of these durations. Ahlfeld's mean of 271 days, and Siegel's of 270 days are shorter than Nürnberger's of 273 days. No doubt the reason lies in Nürnberger's inclusion only of durations of 250 to 300 days, whereas Ahlfeld's durations fall between 238 and 320 days, and Siegel's between 238 and 308 days. Nürnberger found a standard deviation of 8.1 days. Ahlfeld's standard deviation, on the other hand, is 12.5 days. This difference also probably may be accounted for by the inclusion of longer and shorter durations among Ahlfeld's cases.

The standard deviation from the mean of Ahlfeld's menstruation-to-birth durations; namely, 13.3 days, was only slightly longer than among the coitus-to-birth durations. The difference between these variances was less than the standard error of the difference, showing that while coitus-to-birth seems to be a little more accurate way of predicting duration, 155 cases, at least, are not enough to bring out a significant difference in the reliability of the two ways of calculating duration of pregnancy.

DURATION OF NORMAL PREGNANCY OF NEGROES AND OF MEXICANS

After finding the mean and standard deviation of normal pregnancy among members of the white race, we were interested in the corresponding figures for the 28 Negro and 56 Mexican cases of durations 254-319 days respectively. The mean duration of normal pregnancy among our Negro cases we found to be 276.3 days, five days less than our mean of 281.4 days for white persons, with a standard deviation of 9.2 days compared to 10.8 days for white persons. Meyer, it will be recalled, had found a difference of 3 days between the two means in his larger number of cases.

The mean duration of normal pregnancy among our Mexican cases was 277.3 days, 4 days less than the mean for our white patients, with a standard error of 14.4 days, 3 days longer than that for white persons.

Both means are significantly different from that for Caucasians, the mean for Mexicans being less markedly so, however, than that for Negroes. As is to be expected among cases of a mixed race, such as the Mexican, the standard deviation is distinctly larger than for white persons. On the other hand, the Negroes, who are also often of mixed blood, were not enough more variable than the Caucasians to enable our small sample of 28 to bring out any significant difference in this respect.

DURATION OF PREGNANCY WHEN EARLY CASES ARE INCLUDED

We next investigated the mean and standard deviation of all pregnancies resulting in living births. This problem indeed is that which first caused us to undertake this piece of research. In an earlier paper on "Causes of Birth Rate Fluctuations,"[14] we assumed that such pregnancies lasted about nine months, and wished now to determine how nearly correct this assumption had been.

Utilizing Schlichting's data (excluding stillbirths), as well as our own, and including all durations of 194 to 329 days, we found means of 279.9 and 276.4 days respectively, with a standard deviation among Schlichting's cases of 19.2 days; among ours, of 15.7 days. A comparison of these means and variances showed that they were markedly different from each other. Here, as in the case of normal pregnancy, we were baffled as to the reason for these differences. Had the 68 cesarean sections and the 73 deliveries prejudiced by venereal disease been included in our cases, our mean duration would have been shorter probably and thus even farther removed from Schlichting's mean duration of 280 days. Abortions and premature births are very common among patients suffering from lues venerea, and cesarean sections are usually performed two weeks before term.

Besides, our mean and standard deviation for normal pregnancy had greatly disagreed with Schlichting's but had nearly coincided with those of Reid and Ahlfeld whose data we had no reason to believe had excluded more of these cases than had Schlichting's. This fact forced us to conclude that some other influence than the exclusion or inclusion of such abnormal cases had intervened to make Schlichting's data different from ours, though not to nearly the same extent that they were different from Meyer's data.

Could it be that Schlichting's data had included perhaps a large number of Hebrews or members of some other race, who though displaying racial differences as to length of pregnancy were more nearly like our Caucasians in that respect than like Meyer's cases, half Negroes and half Caucasian? Or may his cases have been selected from a different social class than either Meyer's or ours?

That his clinic was distinguished by some such feature is further indicated by an analysis of his data on age at onset of menses published in the same paper[15] with his data on duration of pregnancy. Schlichting had

procured from his Munich clinic and published in this paper the age at onset of menses of 8881 cases, including 1641 patients born in Munich. He also published in this paper a table showing the age at onset of menses of 3114 patients treated at Hecker's[16] clinic in Munich including 1072 patients born in Munich. Although the data from both clinics were gathered in the same two decades and in the same city, the χ^2 test showed no homogeneity between them. Indeed there was much more evidence of homogeneity between Schlichting's Munich data and certain Berlin data gathered by Krieger[17] at about the same time than there was between the two tables of Munich data.

It would be illuminating to know what the distinguishing feature of Schlichting's clinic was. At any rate, we can be certain that something marked off his cases from the others we have been studying, which was reflected both in the proportions at varying ages of onset of menses and in the average duration of pregnancy.

INFLUENCE OF AGE AND OF NUMBER OF PREVIOUS PREGNANCIES UPON DURATION OF PREGNANCY

In order to estimate how much influence, if any, age of the mother might have upon the length of pregnancy, we segregated from all of Schlichting's 397 cases of durations 234 to 325 days, the cases of first pregnancy between the ages of twenty and twenty-four years. The cases in this subclass numbered in all 106. The mean duration of the subclass was 280.3 days with a standard deviation of 14 days. The mean duration of the other 291 cases in this sample was 280.4 days, also with a standard deviation of 14 days. The difference, 0.1 day, between the means is only one-fifteenth of its standard error. These results provided almost perfect proof that age and parity have no influence upon duration of pregnancy. (It is well known, of course, that child-mothers and very aged mothers are apt to terminate their pregnancies early, but there were no such cases included in our study. But their comparative infrequency would make our statement as to the influence of age upon duration of pregnancy still generally true.)

Notwithstanding these results, we wished to investigate further the influence of parity upon length of pregnancy, on account of the old wives' tale to the effect that first pregnancies are usually longer than later ones. Accordingly, we examined the histories of 52 of our cases in which the duration of a first pregnancy could be compared with the durations of later pregnancies. The mean duration of the 52 first pregnancies was 277.2 days; that of the 61 later pregnancies was 276 days. The difference between these means as well as between the variances about the means could not be judged significant on the basis of this small sample. The sample makes it clear that if there really is a difference in length, then first pregnancies are not more than about 8 days longer and not more than about $5\frac{1}{2}$ days shorter than later pregnancies. This evidence, coupled with that in Schlichting's larger sample, seems to show that the

number of previous pregnancies has little or nothing to do with the length of term.

INDIVIDUAL DIFFERENCES AS TO LENGTH OF PREGNANCY

Krahmer's[18] observations on cows show that individuals differ greatly from each other in average length of pregnancy. By analogy, it has often been argued by other writers that human mothers must so differ from each other.

We found Ahlfeld's[19] data portraying such comparisons between women too meagre to use, and so gathered from our Lane Hospital histories the cases of 89 mothers who had had more than one delivery in which the duration of pregnancy could be calculated. Among these 89 persons, 194 pregnancies were recorded. The mean for all these 194 durations was 277.7 days; the mean durations for the individual mothers ranged from 246 to 304 days. The standard deviation of deviations from the individual means was about 15 days, but the standard deviation of all the individual means was 19 days. In other words, the durations of successive gestations in the individual mother differed, in general, much less from the average for that mother than from the average for all 89 mothers.

These findings[20] are summarized in Table VII.

TABLE VII.   COMPARISON OF INDIVIDUAL WOMEN AS TO AVERAGE
LENGTH OF PREGNANCY

	SUM OF SQUARES OF DEVIATIONS FROM MEAN—(I)	DEGREES OF FREEDOM (II)	ESTIMATE OF VARIANCE, s^2 (I)/(II)	STANDARD DEVIATION, s
Within classes	23,186.2	105	220.82	14.9 days
Between classes	32,539.9	88	369.77	19.2 ,,
Total	55,726.1	193		

The variances here are greater than in the other samples on account of the inclusion of stillbirths among the pregnancies. But the difference between the variances of Table VII we found to be very significant, making it clear that there is greater variability among different persons as to duration of pregnancy than there is among different pregnancies in the same woman.

SKEWNESS AND KURTOSIS OF DURATION OF PREGNANCY CURVE

Fig. 1 shows the distributions of Schlichting's and our data respectively when the ordinates represent the number of cases and the abscissae the various durations of pregnancy. It is obvious that in both cases the distributions are not symmetrical about the mean, more cases falling to the left of it than to the right. While it may at first appear paradoxical that anything should be less than its mean oftener than greater, such is actually the case with duration of pregnancy. The distribution shows a skewness because of the scattering of early births, which shade by imperceptible degrees from the definitely premature to the normal type.

We shall now consider the implications of the shapes of these distributions for theories of the relation of menstruation and the beginning of pregnancy.

The third moment of a frequency distribution is the mean of the cubes of the deviations from the mean, and the fourth moment is the mean of the fourth power of these deviations. The *skewness* is defined as the ratio of the third moment to the cube of the standard deviation; the *kurtosis* is the ratio of the fourth moment to the fourth power of the standard deviation. Upon the basis of particular theories regarding the
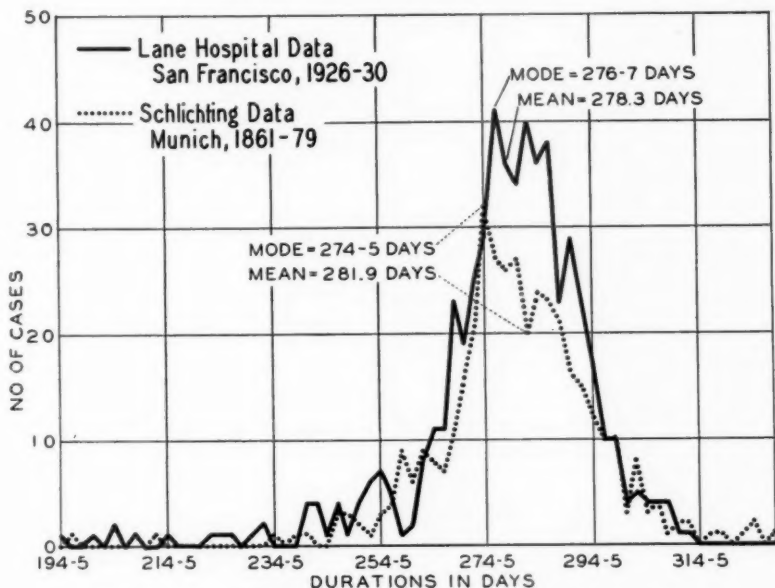
Fig. 1.—Frequency distributions of durations of pregnancy.

relation of pregnancy and menstruation, values for the skewness and the kurtosis can be calculated, and can then be compared with the values actually obtained.

If conception always took place at approximately the same stage of the menstrual cycle, and if the duration of pregnancy depended only on a large number of independent causes contributing approximately equal portions of its variance, the distribution would be of the "normal" form so often discussed in statistics. The skewness of the normal distribution is zero, its kurtosis exactly 3.

If conception took place at random at all stages of the menstrual cycle with equal probability, and if the time from conception to birth were the same in all cases, the skewness would be zero and the kurtosis 1.8, while the standard deviation would be the ratio of the length of the menstrual month to the square root of twelve, or about eight days.

If we compromise between the two hypotheses and regard conceptions as scattered with uniform density through the month and the interval from conception to birth determined by a large number of other chance

variables, each contributing very little to the total variation, we shall have a kurtosis between 1.8 and 3.0 and a standard deviation greater than 8 days, while the skewness will still be zero.

All these theories are inconsistent with the actual data. The standard deviations of menstruation-to-birth intervals given in Table VI are indeed sufficiently large to permit of uniform scatter of conception through the menstrual month, with some additional variation. But the kurtosis of Schlichting's data is 4.9; and a calculation based on all the data assembled from Lane Hospital records, with rejection of several unusual types of cases such as non-white races, but with inclusion of the shorter durations, gave for the kurtosis the surprisingly high value 8.06. The standard error for each of these kurtoses was only about 0.24, making it clear that even so low a value as that for the normal curve is entirely unacceptable. Not only is there no support for the hypothesis that the beginning of pregnancy is randomly distributed through the menstrual month, but the kurtosis shows the opposite type of deviation from the value to be expected on the basis of purely random duration. It is plain that an excessive kurtosis exists which demands explanation. Likewise the skewness has in each case a negative value far outside the limits reasonably to be expected in random sampling. Schlichting's material has skewness −1.09, while ours has skewness −2.57; the standard errors are 0.118 and 0.125, respectively.

One possible source both of skewness and of kurtosis is in the mingling of two distributions of similar character but with different means. Such a mingling might result from an error of one menstrual month in a fraction of the cases, due either to a "false menstruation" after the beginning of pregnancy, or to an error in dates, giving the date of an expected menstruation which failed to occur in place of that of the last actual menstruation. If p is the proportion of cases in which such an error is made, and if w is the ratio of the length of the menstrual month to the standard deviation of the mingled distribution, the kurtosis of the true distribution would be increased by

$$(p - 7p^2 + 12p^3 - 6p^4)\, w^4.$$

At the same time the skewness, measured by the ratio of the third moment (i.e., the mean cube of the deviations from the mean) to the cube of the standard deviation, would be changed by

$$(p - 3p^2 + 2p^3)\, w^3.$$

The value of p which makes the kurtosis arising in this way a maximum is $\frac{1}{2} - \sqrt{6}/6 = 0.0917$, and corresponds to an added kurtosis of $w^4/24$.

If the mean time from the last true menstruation to the false menstruation is no more than 28 days, then since the standard deviation of pregnancy durations cannot possibly be taken less than 10.5 days, w cannot be more than 8/3. In this case the limit $w^4/24$ is only sufficient to increase the kurtosis from the value 3.00 appropriate to the normal distri-

bution to 5.11.   The kurtosis of Schlichting's cases is within this limit, but the whole of the kurtosis in our San Francisco data cannot be accounted for in this way, unless the mean interval from true to false menstruation is somewhat greater than the normal intermenstrual period.

By equating the expressions above for the excesses of skewness and kurtosis above those of a normal distribution to the excess values actually found, a pair of equations is obtained for determining p and w.   Dividing one by the other shows that w is uniquely determined if p is.   When w is eliminated between the two, an equation of the sixth degree in p is obtained.   The roots of this equation always fall into pairs whose sum is unity, and this fact makes it possible to reduce it to a cubic.   There are, in fact, always two and only two roots between 0 and 1; these may be distinguished from each other by the sign of the skewness.

Upon applying this process to our San Francisco data, we find as the solution that 9.12 per cent of the cases had the false menstruation, while $w = 3.33$.   Since the standard deviation was 15.86 days when short durations were included, this suggests a period of 53 days between true and false menstruation, which seems excessive.   If the standard deviation 10.7 days, found by rejection of durations less than 254 days, be used, the period in question becomes 35 days.

Schlichting's cases indicate in the same way that the false menstruation occurred in 7.42 per cent of the cases, with $w = 2.62$.   The period indicated by the same process as our 35 days is 32.5 days.

These determinations are of course subject to random sampling and other errors.   To investigate adequately their accuracy would be a mathematical problem of some complexity; indeed, no one has ever obtained the general sampling distribution of a root of a cubic equation.   However, it appears fairly clear that all but a small amount of the observed skewness and kurtosis can be accounted for on the hypothesis of a false menstruation occurring somewhat more than 28 days after the last true menstruation in a proportion of cases ranging between 7 and 10 per cent. The distribution form also seems to require that pregnancy be regarded as beginning with menstruation, or some time fixed with respect to menstruation, not with coitus.

Rather less light than might be expected is thrown on the explanation of kurtosis by Ahlfeld's 155 cases in which the date of coitus was known. The standard deviation is indeed greater than that for the San Francisco menstruation-to-birth material, which is to be expected if the beginning of pregnancy is fixed with reference to menstruation rather than coitus; but it is less than Schlichting's, and the differences are not great enough to be significant.   The negative skewnesses noted are for Ahlfeld's cases replaced by the small positive value 0.384, which is not quite double its standard error.   However, the kurtosis has the high value 5.21.   This may be explained by the peculiar distribution of intervals from menstruation to coitus in these cases, which has kurtosis 4.77, together with the possibility that pregnancy is to be regarded as beginning in a

minority of cases with the menstruation next after coitus rather than with that preceding. This last hypothesis would also explain the slight positive skewness.

SUMMARY OF FINDINGS

The conclusion of the earlier writers that 280 days is the average duration of normal pregnancy; that is, when the very short and very long durations are excluded, is confirmed by our study. However, the standard deviation from this average which other students have estimated to be from 8 to 10 days, we find to be 11 days. If the early births are included, the mean duration is shorter and the standard deviation greater.

The mean duration from date of coitus to birth is 271 days, the standard deviation being scarcely any less than when duration is counted from the beginning date of the last menstruation. The standard deviation also seems to be no less when duration is counted from the last day of the last menstruation, as in England and France. Accordingly, there is no perceptible gain in accuracy by reckoning even from a single coitus of known date, unless, of course, the menstruation date is unknown.

For different races both the mean durations of pregnancy and the standard deviations are significantly different. However, contrary to the opinion of Labouré,[22] the mean and standard deviations are practically unchanged if cases such as stillbirths, cesarean sections, and those influenced by venereal disease are excluded.

No significant difference appears either in mean length or in standard deviation between first and later pregnancies. Age of the mother seems likewise to be without effect.

In support of the argument from analogy with cows, horses, and other animals, that individual mothers differ greatly from each other in average length of pregnancy, we prove from the records of 89 individual mothers who were delivered of more than one child at Lane Hospital in San Francisco that the differences between the average pregnancy durations of individuals are significantly greater than the differences between the various pregnancies of each individual.

Contrary to the belief of some writers that the frequency curve of durations is normally distributed, with just as many deviations of each magnitude on one side of the mean as on the other, we find that it is really far from normal, with the cases concentrated about the mean in such a way as to indicate some variable disturbing factor other than the date of impregnation.[23]

In fact, it appears from the shape of the curve that it is safe to assume in predicting the time of birth that the birth is more likely to occur *before* the average time than after it.

A large part of the abnormality of the curve may be explained on the hypothesis that approximately 10 per cent of the menstruation-to-birth durations were really one month longer, due perhaps to a "false menstruation" occurring after pregnancy had actually begun. But in order

to make these actual durations fall into a theoretically normal distribution, it must further be assumed that the "false menstruation" occurred not 28 days after the last true menstruation, but 32-35 days later.

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ECLAMPSIA WITHOUT CONVULSIONS OR COMA

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HISTORICAL

THIS apparently paradoxical title probably finds the basis of its seeming contradiction in the fact that clinical experience in the vast majority of eclamptic cases has so firmly fixed the symptoms of convulsions and coma in the concept of eclampsia that, in the minds of some, they are acceptedly inseparable. Thus Seitz, in 1909, reporting a case of eclampsia without convulsions and reviewing some of the literature, states specifically that the only *unfailing* symptom of the malady is coma. Unfortunately his review of the literature must have been incomplete, since five cases lacking both convulsions and coma, and proved by autopsy, had been reported previous to 1909. Since that time an additional case has appeared in the German literature and one in the French. The purpose of the present writing is to report still another case of this relatively common disease occurring in this relatively uncommon form.

The fallacy of considering convulsions and coma an essential component of the eclamptic syndrome has long and adequately been warned against by J. Whitridge Williams, in his textbook "Obstetrics."

Slemons, in 1907, wrote what is probably the most thorough and comprehensive review of eclampsia without convulsions to be found in the English language. He

mentioned seven cases, proved by autopsy, to which sum he added two cases observed on the Johns Hopkins Hospital service. Liebmann (1925) mentioned forty-one autopsy proved cases. He offers in explanation that many other cases have been reported under the diagnosis of eclampsia without convulsions in which recovery occurred or autopsy was refused. None of these cases are considered in his series. Caffier (1927) submitted a case report in which he included a bibliographic résumé of thirty-eight cases authenticated according to the above standard.

These citations suffice to establish the condition of eclampsia without convulsions as a repeatedly observed and verified clinical fact. However, in most of these cases coma was an outstanding feature. A review of the literature available to date discloses only seven cases reported in which both convulsions and coma were absent. The chronologic sequence of the latter reports is Klebs, 1888; Bouffe de Saint Blaise, 1891; Wendt, 1898; Poten, 1906; Chirie and Stern, 1908; Schmid, 1911; and Chatillon, 1917. These cases are remarkable for their rarity and unique in the total absence of what ordinarily constitutes cardinal symptomatology in the disease concerned. The following case was felt to merit report as one fitting into this classification.

CASE HISTORY

Mrs. I. M., 6414, aged twenty-one, primipara, thirty-three weeks gestation, admitted to hospital February 6, 1931, 9:00 P.M., complaining of headache, dimness of vision, and slight edema of hands and face. Nothing unusual in family, past, menstrual, or marital history.

Her pregnancy was uncomplicated until two months ago when albuminuria appeared. Subjectively well until six days ago when puffiness of face appeared, three days ago severe frontal headaches, definite decrease in urinary output; very slight edema of hands and feet during last twenty-four hours. Fetus living.

Catheterized uncentrifuged urine showed: Large amount of albumin; 20 to 30 W.B.C., occasional R.B.C., and 4 or 5 hyaline casts per L.P.F. The blood showed R.B.C., 5,030,000; W.B.C., 10,200; platelets, 367,000; plasma volume, 2560 c.c. or 3.99 per cent of body weight; blood volume, 5120 c.c. or 8.14 per cent of body weight.

February 7: Marked clinical improvement, no headache, vision better, edema less. P.S.P. 25 per cent first hour, 20 per cent second hour, total 45 per cent. Irregularity of nail-bed capillary flow. Diet: Fruits and fruit juices.

February 8: No complaints in morning. Eye-ground examination. Picture of fairly early hypertension. Nausea and vomiting once in evening.

February 9: Comfortable, slight nausea and vomiting. Sore throat, negative to inspection. Capillary flow irregular. Restless in early evening. Poor night.

February 10: Epistaxis, nausea, vomiting. Recurring edema of hands and face and dimness of vision. Irritability, headache, epigastric pain.

Bag induction. Ecchymotic spots at site of needle punctures. Icteric tinge. Delivery five hours after bag was inserted; 2000 gm. stillborn fetus. Minimal blood loss. Marked drop in blood pressure, temporary rise with intravenous glucose and acacia, gradual decline to shock levels. Death one hour postpartum without patient having had convulsions or being in coma.

Highest temperature while in hospital 37.2° C., highest pulse was (admission) rate of 96 with exception of the terminal shock elevation.

LABORATORY

Complete blood examinations were made, but only the significant data are incorporated in Table I.

TABLE I. BLOOD CHEMISTRY FINDINGS

DATE	PER CENT			MG. PER CENT		VOL. PER CENT CO_2	P_H
	HB	CELL VOL.	SER. PROT.	N. P. N.	CHOL.		
2-6-31	125	50	5.8	43	734	49	7.47
2-7-31	125	50	6.3	26	518	45	7.40
2-8-31	111	39	4.2		270	45	
2-9-31	105	40	4.1	23	390	47	7.45
2-10-31	118	47	5.4	25	250	46	7.40

There was a slight retention of nitrogen which disappeared as soon as a diuresis was established. The marked concentration was not relieved by the glucose injection as the protein percentage was still high the following morning. There was a 20 per cent to 25 per cent increase in blood volume following the administration of acacia solution as determined by the drop in hemoglobin, cell volume, and serum protein. This hydration persisted for seventy-two hours before water was again being lost from the blood.

An increased serum cholesterol is characteristic of the toxemias of pregnancy but

TABLE II. RESUME OF CLINICAL COURSE, TREATMENT, AND URINARY FINDINGS

DATE	CLINICAL CONDITION			TREATMENT	URINE		
					AMOUNT C.C.	CHLORIDES	
	T. P. R.	WT.	B. P.			GM.	PER CENT
2-6-31 12 hr.	Headache Edema Drowsy Eye Signs 37°-96-20 66 K		176/130	1000 c.c. 20% Glucose 1000 c.c. Diet ———— 2000 c.c. Total	1800	0.91	0.065
2-7-31	No Headache Less Edema Improved Vision 36.5°-82-18		175/140	1000 c.c. 6% Acacia 2700 c.c. Diet ———— 3700 c.c. Total	3200	2.97	0.110
2-8-31	Well 36.7°-88-20 65.8 K		178/140	2930 c.c. Diet ———— 2930 c.c. Total	1800	2.64	0.120
2-9-31	Slight Nausea Restless 36.5°-88-22		185/140	3050 c.c. Diet ———— 3050 c.c. Total	1900	0.64	0.032
2-10-31	Nausea and vomiting Headache Epigastric pain Epistaxis Edema 36.5°-90-18 67.1 K Delivery Death		195/160	1600 c.c. 20% Glucose 6% Acacia 850 c.c. Diet 2450 c.c. Total	900		

this was one of the highest ever found by us. No explanation is offered for the tremendous drop unless the pathologic lesions of the liver are responsible.

The acid-base balance was always normal.

Fig. 1.—Gross specimen of liver; anterior surface showing marked involvement of the liver with hemorrhage. Typical eclamptic liver in the gross.
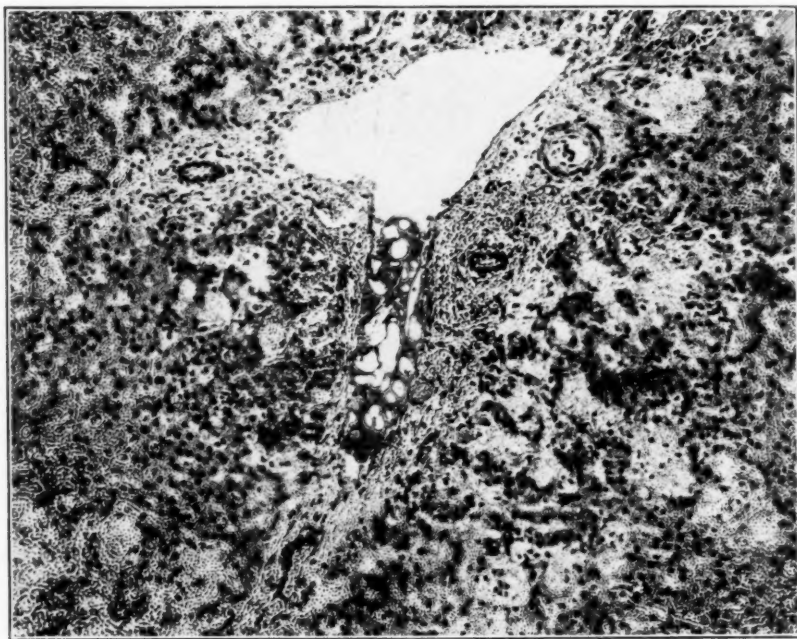

Fig. 2.—Shows small portal space with portal vein, hepatic artery, and bile duct. Note marked extravasation of blood into periportal tissue as well as into the distended sinusoids. The red blood cells are in great part hemolyzed.

Table II illustrates the marked increase in urinary output and chlorides after the acacia injection.

The most important single feature brought out in the observation of this case was the striking clinical improvement coincident with the hydration of the blood and the return of unfavorable symptoms with the return of blood concentration.

PATHOLOGY

Autopsy was performed by the Department of Pathology immediately following death. For the sake of brevity only those portions of the pathologic report relative to the liver and kidney are included.

Gross Description.—The liver weighed 1920 gm. and measured 25 by 18 by 9 cm. It was covered by a smooth capsule which was shiny and glistening. The right lobe
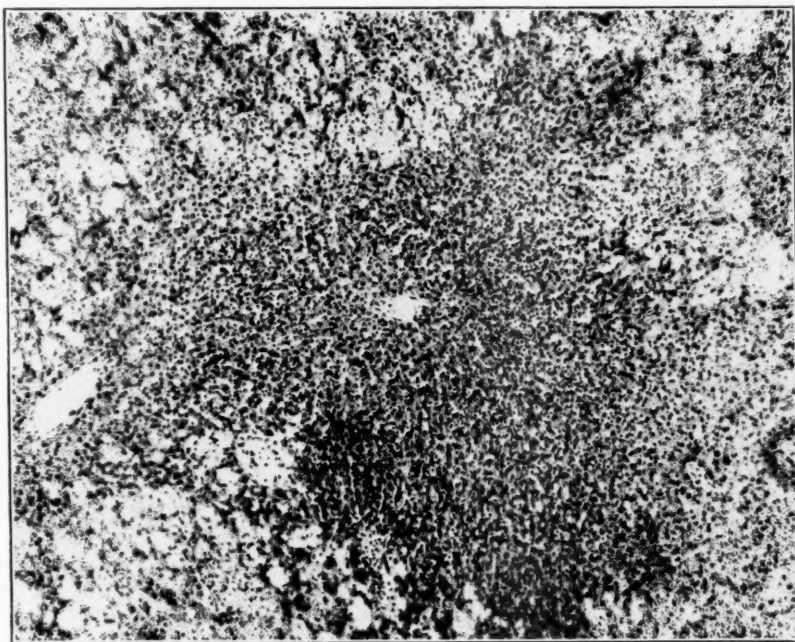
Fig. 3.—Shows marked hemorrhage and destruction of liver tissue in the periphery of the lobules. The central vein in the center of the picture and liver cells immediately surrounding it are normal.

appeared to be projecting prominently above the rest of the anterior surface of the liver. The superior surface of the anterior view showed a mottling of reddish to brown blotches which varied in size from pinpoint to confluent areas, one-third to one-half the size of the palm of the hand. There was one very large area of brownish hemorrhagic appearance over the lower part of the anterior surface which was 8 cm. in diameter. Radiating out from this large area were smaller projections which appeared as an interlacing network over almost the entire anterior surface of the liver. All the area between these hemorrhagic areas was yellow. To palpation the hemorrhagic areas were quite solid, while the yellow areas were softer and slightly depressed. The left lobe had the same appéarance, and there were only several places on this anterior surface which did not show the hemorrhagic blotches. Adjacent to the fissure formed by the falciform ligament and extending right to the bare area of

the liver forming a V, there was a solid area of hemorrhage which seemed to follow a line around the periphery of the bare area on the superior surface.

Viewed from behind the gastric depression showed the discoloration noted on the anterior surface. The tuber omentale just to the right of the gastric depression was raised and mottled with extensive coalescing hemorrhagic spots. The caudate lobe was practically all covered with the hemorrhagic blotches. The quadrate lobe contained a great number of hemorrhagic areas but not as many as the caudate lobe. The posterior surface of the right lobe appeared to be very shotty with the hemorrhagic areas. This hemorrhagic mottling was most particularly noted near the inferior vena cava fossa. This particular distribution of the hemorrhagic areas was also noted on the left lobe from behind near the fossa for the ductus venosus. There was an appreciable increase in hemorrhage near the fossa for the umbilical vein as well.
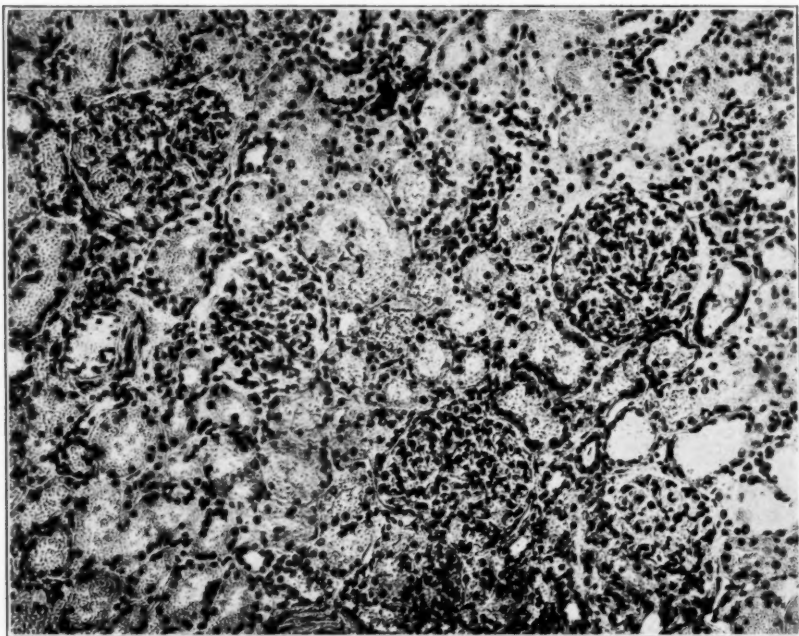

Fig. 4.—Kidney. Shows the convoluted tubules in a state of hyaline degeneration. The cells of the glomerular tufts are markedly swollen causing the glomerulus to fill out the entire capsule. This picture is similar to that described by Fahr as being typical of eclampsia.

Each kidney weighed 170 m., and measured 11 by 6.5 by 4.5 cm. The capsule was smooth and free from any adhesions. On cut section the capsule retracted readily; it stripped easily from the cortex leaving a smooth but pale cortical surface. The cut surface of the kidney was pale and appeared markedly swollen. The right ureter was dilated in about its middle third, apparently due to pressure by the pregnant uterus.

Microscopic Description.—The liver showed many interesting things which were brought out by Mallory connective tissue stain. In the hematoxylin and eosin stain, one saw areas of blood around the portal spaces. Many of these areas appeared to be simply distended capillaries or sinusoids filled with blood cells, but with the connective tissue stain one saw that the blood was definitely outside the capillary lining of the sinusoids. The capillaries were seen as flat endothelial tubes compressed by collections of red blood cells outside the capillary walls. The endothelial cells of

the capillary walls appeared to be tremendously swollen. Other areas showed a definite degeneration of the liver cord cells with areas of hemorrhage scattered throughout the degenerated cells of the liver cords. However, many of the areas did not show much degeneration of the liver cells. In the liver one saw that many of the capillaries contained thrombi of red blood cells which appeared to be agglutination thrombi.

With a Mallory connective tissue stain of the kidneys one saw that the epithelial cells which covered the glomerular tufts were tremendously swollen, standing out as globular dark blue cells over the capillary tufts. In many of the collecting tubule cells one saw free hemorrhage. All of the capillaries were markedly engorged with blood cells. Many of the tubules contained hyaline casts. Many of the tubule cells were seen to be in a stage of hyaline degeneration. There was extreme cloudy swelling with albuminous degeneration of the tubular epithelium. In the space between the glomerulus and capsule of Bowman in many instances one saw a pink staining material which resembled fibrin. There was an extreme congestion.

Anatomical Diagnoses.—(1) Eclampsia gravidarum; (2) thrombi in branches of portal vein with areas of hemorrhage; (3) cloudy swelling of kidneys.

SUMMARY

1. An unusual case of eclampsia without convulsions or coma is reviewed with special reference to some of its most outstanding clinical, laboratory, and postmortem features.

2. Attention is again called to the prime importance of establishing and maintaining blood dilution in eclampsia.

3. A possibly much more adequate therapeutic agent (acacia) for producing a more lasting hydration of the blood is suggested.

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A STUDY OF BLOOD AND URINARY AMYLASE IN PREGNANCY AND ITS LATE TOXEMIAS

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NUMEROUS studies have been made upon a starch splitting ferment present in the blood, urine, and feces. According to most workers, the principal source of this amylase is the pancreas,[1] and from this organ the ferment gains entrance to the intestinal tract and blood, and is excreted in the feces and urine.[2] In a review of the literature, one is struck by the varied results and conflicting opinions. The urine has shown marked fluctuations, but determinations made upon the feces have shown such wide variations, that no normal value can be accepted. However, fairly constant quantities have been found in the blood.

In the normal individual, Cohen[3] found fairly constant quantities in the blood, but marked variations in the urine. Digestion seemed to play a part in the rise, in that amylase was absorbed into the blood and quickly excreted in the urine. Reid[4] found diurnal variations in healthy subjects. Higher values were obtained from night specimens of urine, the diastatic value being found to vary inversely with the rate of excretion, and directly with the specific gravity. Some variation was found in the blood, the lowest level occurring from the fourth to eighth hour following a meal. In cases of chronic kidney disease, there was a lowered amount in the urine, while in some cases of acute nephritis, the amount was raised.

Both Stocks[5] and Block[6] arrived at similar conclusions, and attempted to put some importance upon this test as a measure of kidney function, in that secretory damage diminished the amount in the urine, and raised the quantity in the blood.

Corbett[7] found the urinary amylase usually greater than that in the blood. With a rise in the blood amylase, there was an associated rise in that of the urine. He considered, that when the serum value exceeded that of the urine, there was evidence of renal insufficiency. He found that ordinary changes of diet, the reaction of the urine, the presence of bacteria, or any other abnormal constituent except blood, produced no alterations in amylase values.

Corbett also states that there was no change during pregnancy or the puerperium, but there was a rise in urinary amylase in cases of eclampsia, with a return to normal during the period of recovery. He explains this high urinary value found in eclampties by amylase leaking through with the albumen which has required no renal activity for elimination. Piano[8] also found that a rise in the blood caused an increase in the urine. In tracing these values through pregnancy, he found a gradual rise up to parturition, with a drop to normal or below during the puerperium. By employing a diastatic index of both blood and urine values, he attempted to estimate renal function. Wallis[9] placed considerable prognostic and diagnostic importance upon diastatic determinations of the urine, in the differential diagnosis of the toxemias of pregnancy. There was a diminution in nephritis, but an elevation in the other toxemias. These changes he found to take place early in the clinical course, and persist for some time afterwards.

In estimating kidney function, Stafford and Addis[10] concluded that blood and urinary amylase determinations were of little value. They found no diurnal varia-

tion in diastatic excretion, and no relation to pancreatic activity. In cases in which a large proportion of the kidney tissue was rendered functionless by disease, there was a decrease in the urinary output of amylase. McClure and Pratt[11] found marked variations in the urine and feces and concluded that these determinations were of but slight value. Elman[13] has shown that disfunction of the pancreas alters the amylolytic content of the blood plasma, which remains within normal limits in the healthy individual.

Perhaps some explanation of the conflicting results obtained lies in the variety of methods used for these determinations. In general these methods did not determine the complete chain of activity of the enzyme.[13, 14] The starch iodine reaction measures the activity of the ferment only to the disappearance of the starch molecule, while the copper reduction method measures only the sugar forming property. Elman and McCaughan[15] adopted a method which does determine the entire chain of activity, by measuring the reduction in viscosity of a starch solution when acted upon by the ferment.

In brief, the technic[15, 12] consists in measuring the time required for a 3 per cent starch solution, containing Sörensen's fifteenth molar phosphate buffer at a P_H of 6.8, to flow through an Ostwald viscosimeter tube kept at a constant temperature of $37.5° C. \pm 0.1° C$. This reading, usually about forty-five seconds, is taken as the zero point. The enzyme is supplied by the addition of 0.4 c.c. of blood plasma to the test solution in the tube. Digestion of the starch progresses with time, thereby reducing the viscosity. An arbitrary end point is chosen at 20 per cent reduction of the initial viscosity, and the unit defined as that amount of enzyme in 1 c.c. that will accomplish this in one hour. To avoid the expression of units in the value of time alone, the factor of concentration is added to Arrhenius' rule. In this formula A.U = 60/T.V., A.U equals amylase units per cubic centimeter, T the time in minutes required to reduce the initial viscosity 20 per cent, and V the volume of enzyme solution added to effect this change.

The measurement of urinary amylase presented some difficulty because the dilution of the starch solution, by the addition of urine caused an immediate change in viscosity. Such a discrepancy in viscosity does not exist between the starch solution and blood plasma. To avoid this error, a zero point reading was taken by adding an inactivated sample of urine (heated to 60 to 70° C. for one or two minutes) to the test solution in the viscosimeter tube. After cleaning the tube, the procedure was repeated in the same one using unaltered urine. It was found that the addition of 0.2 c.c. of urine usually caused the end point to be reached at a convenient time. To avoid any diurnal variations, an aliquot portion of a twenty-four-hour specimen was used. After determining the number of units per cubic centimeter, the total output of units was obtained by multiplying the number of centimeters per twenty-four hours by the number of units per cubic centimeter. For example, if the addition of 0.2 c.c. of urine to 5 c.c. of the starch solution caused a 20 per cent reduction in twenty-five minutes, according to the formula A.U = 60/T.V., then

$$A.U = \frac{60}{25 \times 0.2} \quad \text{or} \quad A.U = 12$$

If the total output of urine in twenty-four hours is 1500 c.c., then

$$12 \text{ U} \times 1500 = 1800 \text{ U}.$$

This figure becomes less bulky if a kilounit is established, whereby the total twenty-four-hour output of amylase units becomes 1.8 K.U.

The above technic was employed throughout the following experiments and each controlled, by either a known normal plasma, or a standardized solution of saliva kept with a crystal of thymol at ice box temperature.

The object of this paper is to determine the blood and urinary amylase during pregnancy, and its toxemic complications. We feel that the method employed by Elman is the most accurate one as yet suggested. We therefore feel that figures obtained by this method will be more reliable than those previously appearing in the literature.

The normal blood amylase for pregnancy was first established in the following manner. Hospital cases were used that showed no clinical evidence of any toxemia, i.e., vomiting, nephritis, preeclampsia, or eclampsia. Determinations were made before, during, and after labor in 25 per cent of the cases. In the remainder, blood was taken at only one or two of these stages. The series consists of 27 cases, upon which 37 determinations were made. The age varied from 18 to 37, and both primipara and multipara were included. The values were found to range from 4 to 7 units per cubic centimeter. Table I shows that the majority occurred between 5 and 6. Considering the normal limits between 4 and 7, these results are practically identical to the normal values found by Elman in healthy individuals, both male and female.

TABLE I. BLOOD AMYLASE VALUES IN NORMAL PREGNANCY

NUMBER OF CASES	NUMBER OF DETERMINATIONS	CONCENTRATION OF AMYLASE UNITS PER C.C.		
		4-5	5-6	6-7
27	37	27%	43%	30%

In ten determinations made upon normal cases during the course of labor, or first twenty-four hours thereafter, there were seven primipara. Four of these seven were not included in the series mentioned, because they showed values of from 9 to 11.5 units. This elevation may be attributed to the long labor experienced by each of these cases, in which a degree of dehydration and starvation was produced.

TABLE II. URINE AMYLASE VALUES IN NORMAL PREGNANCY

NUMBER OF CASES	NUMBER OF DETERMINATIONS	CONCENTRATION OF AMYLASE U. PER C.C.					
		4-10	10-15	15-20	20-25	25-30	30-35
18	22	37%	27%	13%	10%		13%
		TOTAL AMYLASE IN K.U. EXCRETED IN 24 HOURS					
		4-10	10-15	15-20	20-25	25-30	30-35
18	22	22%	13%	23%	23%	10%	9%

In the study of urine values, normal cases of pregnancy were used, the determinations being made before and after delivery in 14 per cent, but only during the puerperium in the remainder. The values varied from 4 to 30 units per c.c., and the total number of units excreted during twenty-four hours from 4 to 35 K. U. Table II shows that the variations were so extreme that no normal values can be accepted for either of these determinations.

Diurnal variations were found in single specimens, and the total output of amylase for the day greater than for the night. The amount of amylase per cubic centimeter was greater in concentrated specimens of urine. Neither P_H readings nor the amount of albumin had any effect on the amount of ferment present. It was found that by the addition of a crystal of thymol the amylase of the urine did not depreciate over several days if kept cool.

Although cases with normal kidney function showed these variations in amylase excretion, it is interesting to note the findings in definite kidney disease. Three cases are presented here to illustrate these results.

CASE 1.—A. S., aged twenty-six, gravida II, entered the hospital at three months' gestation because of hypertension, edema, and albuminuria. Nephritic history with toxemic complications during first pregnancy eleven years before. At this admission the urinary output was very scant, phenolsulphonephthalein eight per cent in two hours and nonprotein nitrogen over 100 mg. per cent. The patient was under treatment for three days when she developed a tingling in the left arm, became comatose, dyspneic, and died. Autopsy showed a hemorrhage about the pons, contracted granular kidneys with almost complete destruction of the cortex, and fluid in the body cavities. The only lesion seen in the pancreas was an intimal thickening of the arteries with an occasional lumen obliterated.

CASE 2.—M. H., aged twenty-three, gravida I, entered hospital one month before term because of hypertension, dimness of vision, edema of face and extremities. Patient delivered spontaneously two days later, passing into a semicomatose condition thereafter. Phenolsulphonephthalein excretion was 10 per cent in two hours, and the nonprotein nitrogen rose to over 100 mg. per cent. The urine contained decreasing amounts of chloride after delivery, albumin, and some casts present throughout. The blood pressure dropped on the eighth postpartum day, and two days later the patient died. Autopsy showed multiple infarcts of the kidneys, adrenals, and small intestines, with an intimal thickening of the arteries of these organs as well as the pancreas and the liver.

CASE 3.—D. T., aged sixteen, gravida I, entered hospital at about three months' gestation because of hypertension and general edema present since the beginning of pregnancy. Spontaneously delivered a premature, stillborn fetus. The nonprotein nitrogen slightly elevated at admission, returned to normal, and the blood pressure dropped slightly. Urine contained some albumin, blood, and casts. General condition improved at discharge. Diagnosed acute nephritis.

The results obtained in these 3 cases are shown in Table III. In the first two cases, there was definite kidney damage. The blood amylase was found to be elevated, and the urine values below any found in normal individuals. Perhaps the most important urinary observation is the low total output of amylase, i.e., 0.25 K. U. in Case 1, and 0.24 K. U. in

Case 2 just before death. In view of the fact that three days before delivery in Case 2, the blood was 8.3 U. and the urine 3.0 U. per c.c. with a twenty-four-hour excretion of 2.17 K. U., one would think there was some kidney damage at that time. As the kidney damage became more severe, the blood value rose to 16.6 U. and the urine dropped to 1.5 U. per c.c. with a twenty-four-hour output of 0.24 K. U. Therefore, it would seem that the greater the impairment to the excretion of amylase in the urine, the higher the value rises in the blood. The rate with which amylase is formed, or gains entrance to the blood need not necessarily be changed.

TABLE III. AMYLASE DETERMINATIONS IN PATIENTS WITH DEFINITE KIDNEY LESIONS

CASE NO.	RECORD NO.	NAME	DAYS ANTE- OR POSTPARTUM*	BLOOD U. PER C.C.	URINE		
					VOL. 24 HR. SPEC.	U. PER C.C.	K. U. PER 24 HR.
1	5449	A. S.		10.0	210	1.2	0.25
2	6057	M. H.	A. 3	8.3	725	3.0	2.17
			P. 10	16.6	160	1.5	0.24
3	4125	D. T.	O.	2.8			
			P. 2	1.7			
			P. 9	2.7			
			P. 13	3.2			
			P. 23	3.7			
			P. 30	3.7			

*Day of determination illustrated by:
A. = Antepartum.   O. = During labor.   P. = Postpartum.

Unfortunately there were no urine determinations made in Case 3, as this patient was observed prior to the time this procedure was adopted. The blood values were consistently below normal, with a gradual increase toward normal as the patient improved. Similar low readings were found in other cases of hypertension. Since the blood amylase was not elevated above normal, it is doubtful if any impairment existed in the excretion of the ferment.

In a series of preeclamptic patients, 31 cases were observed with a total of 66 blood determinations. Upon 7 of these, there were 13 twenty-four-hour urine examinations. Both the blood and urine values were found to be lower than those of normal pregnancy. This is shown by comparing Tables IV and V with I and II.

TABLE IV. BLOOD AMYLASE VALUES IN PREECLAMPSIA

NUMBER OF CASES	NUMBER OF DETERMINATIONS	CONCENTRATION OF AMYLASE U. PER C.C.				
		2-3	3-4	4-5	5-6	6-7
31	66	13.5%	21.5%	32.0%	19.5%	13.5%

No typical value can be established for these cases. If symptoms were of long duration, the blood values were found to be lower than in cases of more recent toxic history. The severity of the disease did not seem to play such an important part. After delivery, the blood value increased toward normal as the patient improved, but the urinary amylase showed such irregularities in concentration and total amount, that a similar observation could not be made. It seems likely that if a hypertension exists for any length of time under the influence of a toxic cause in pregnancy, that vascular changes would take place to alter pancreatic activity, or to diminish the absorption of amylase into the blood. With removal of the toxicity and lowering of the high blood pressure, a gradual return toward normal relationship is established.

TABLE V. URINE AMYLASE VALUES IN PREECLAMPSIA

NUMBER OF CASES	NUMBER OF DETERMINATIONS	CONCENTRATION OF AMYLASE U. PER C.C.			
		3.7-10	10-15	15-20	20-25
7	13	70%	23%	7%	
		TOTAL AMYLASE IN K.U. EXCRETED IN 24 HOURS			
		3.7-10	10-15	15-20	20-25
7	13	56%	7%	30%	7%

TABLE VI. BLOOD AND URINE DETERMINATIONS IN CASES OF PREECLAMPSIA SHOWING THE GRADUAL RISE OF THE LOW BLOOD VALUES TOWARD NORMAL DURING THE PUERPERIUM, AND THE IRREGULAR URINE VALUES

CASE NO.	RECORD NO.	NAME	DAYS ANTE- OR POSTPARTUM*	BLOOD U. PER C.C.	URINE		
					VOL. 24 HR. SPEC.	U. PER C.C.	K. U. PER 24 HR.
1	6805	E. D.	P. 5	2.5	1680	11.5	19.3
			P. 6		1380	15.0	20.7
			P. 8		1000	20.0	20.0
			P. 9	3.5	1200	6.2	7.4
			P. 12	4.0			
			P. 15	5.8	1675	5.4	9.0
2	6842	P. G.	A. 1	2.0			
			P. 2	2.3			
			P. 6	3.3			
			P. 7	3.1	1350	3.9	5.3
			P. 12		1840	3.7	6.8
3	11405	L. McL.	A. 6	4.0			
			A. 1	2.1			
			P. 1	3.2	720	7.0	5.0
			P. 1	3.6			
4	6965	A. C.	A. 36	2.6			
			P. 6	2.1			
			P. 10	2.5			

*Day of determination illustrated by :
    A. = Antepartum.   P. = Postpartum.

Four of these cases are reported with some detail in Table VI. It would seem in the first one, that since the gradual rise of the blood to normal during the puerperium is accompanied by a drop in the urine, that there may have been some impairment in the excretion of amylase The patient showed clinical evidence of steady improvement, and this discrepancy is attributed to the irregularity of the urinary amylase, the exact physiology of which is vague. In Case 3, a normal value was found six days before delivery, but as the toxemia advanced a low value was found on the last day of pregnancy. A slight rise occurred on the day of delivery when a cesarean section was done. The patient died rather suddenly from an unexplained cause, possibly an embolism. No postmortem examination was permitted.

It naturally follows, that if preeclampsia shows these low values, one would expect to find even lower values in eclampsia. The eclamptic series consists of 5 cases. These all showed very low values except one, in whom the disease developed rather suddenly. The study of this type of toxemia cannot be considered complete as yet.

The highest values in both blood and urine that have been observed, except in pancreatic disease, were found in cases of vomiting. This study is not sufficiently complete to allow an explanation, and is only mentioned at this time.

DISCUSSION AND SUMMARY

In a study of 71 cases of pregnancy, 112 blood and 38 urine samples were examined for their amylase content. The blood was taken either before, during, or after labor, and the urine from an aliquot portion of a twenty-four-hour specimen. The technic for these determinations was the same as described by Elman and McCaughan, which employs the change in viscosity of a starch solution when acted upon by the ferment. The principle of this method affords more accurate results than those with other quantitative tests. In addition to determining the concentration of amylase units per cubic centimeter of urine, the total amount excreted per twenty-four hours has been expressed in kilo units.

From the results it has been shown that during normal pregnancy the blood amylase remains unaltered and within constant values of 4.0 to 7.0 units per cubic centimeter. These limits are the same as found in healthy individuals both male and female. However, in some primiparae with a long labor, there may be a slight rise at parturition. It is believed that this is due to dehydration, thereby concentrating the blood, and starvation, in which an increased amount of amylase would be employed for the breaking down of polysaccharids such as liver glycogen.

The urinary amylase of normal pregnant women varied both in concentration and total amount excreted per twenty-four hours. Marked diurnal variations were found, and a larger total amount excreted during the day than night. Variations were not only found in different individuals, but the same patient excreted varying quantities on different

days. Neither the P_H, nor presence of albumin had any relation to the amount of amylase present. No characteristic change was noted in such complications as cystitis, pyelitis, acute endometritis, acute mastitis, nor in mild thyrotoxicosis.

The ferment was found to be in larger amounts in concentrated specimens, but even in those of large volume, in which the amylase was diluted, the concentration was equal or greater than that found in the blood. It is evident that the excretion of amylase by the kidneys plays some part in the regulation of the constant blood levels. If the kidney function is normal, the ferment is always present. When severe kidney damage exists, with a marked loss of secretory tissue the elimination of amylase is impaired and the concentration in the blood rises. This is illustrated by two cases, one with contracted granular kidneys, and the other with multiple renal infarcts. The amylase apparently leaks through in acute nephritis, however, as no rise was found in the blood of such a case.

If, on the other hand, the amount of amylase entering the blood is actually increased and the kidneys normal,* a tremendous increase is found in the urine. If an amount above normal is demonstrated in the blood, then the rate of entrance to the blood stream must be greater than the rate of excretion of the excess, and it would seem that the kidneys have an upper threshold at which they function efficiently to help maintain a normal blood level. Any increased rate of excretion that they may compensate for, under pressure, is not of the same progression as that within the limits of normal, unless there be some reaction to prevent its excretion when present in a large amount, should this quantity be of physiologic importance.

The existence of an antiferment is fairly well disproved, so it is not likely that any process of conservation would take place. However, according to Sherman[16] and Caldwell,[17] most amino acids conserve amylase from hydrolytic destruction, and increase its activity. They believe the ferment itself to be of a protein nature, or contain protein as an integral constituent.

In preeclampsia low blood values were not uncommon, with a gradual rise toward normal after termination of the pregnancy. The duration of toxic symptoms seemed to be of more importance than the immediate severity. The urine values fell within wide variations, but if considered as a group the general average fell below that for a corresponding group of normal cases. This is to be expected since a lower blood value necessarily would diminish the excretion. The same findings occurred in eclampsia, with even lower values, except in one case that developed rather suddenly. Kidney damage apparently was not severe enough in any of these cases to cause any block in amylase excretion. In such complications the blood contains less of the ferment than normal, so there

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*This was seen in some cases of vomiting in pregnancy not reported at this time, and in certain pancreatic conditions.

must be a decreased amount entering the blood stream. This impairment may be explained on a basis of vascular changes in the pancreas. After termination of the pregnancy, there is some gradual readjustment that allows a slow return of the blood amylase toward normal.

Whether or not the pancreas takes any part in these toxemias of pregnancy has neither been proved nor disproved, but there are certain changes that take place in the amylase content of the blood in these conditions. It does not seem that amylase determinations are of any great diagnostic or prognostic value, but have some importance in an investigative study of these toxemias. The amylase values will be altered by the kidneys only when there is severe loss of renal function, which causes some impairment of amylase excretion.

CONCLUSIONS

1. Normal pregnancy has no effect upon the blood amylase, which remains between 4 to 7 units per c.c., which is comparable to the limits previously found in the nonpregnant individual.

2. The urine shows such wide variations both in concentration of units and total amount excreted in twenty-four hours that no normal figure can be given.

3. A slight rise may occur in the blood during labor if the process is long and difficult.

4. The excretion of amylase by the kidneys is not impaired unless there is considerable loss of secretory tissue.

5. In the cases of toxemia of pregnancy with a hypertension that were examined, 35 per cent of the determinations showed a blood amylase value distinctly below normal.

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BLOOD CHEMISTRY STUDY IN NORMAL PREGNANCY AND ECLAMPTOGENIC TOXEMIA*

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THE various changes in the chemistry of the blood during pregnancy have attracted the attention of numerous investigators, since a knowledge of such changes might be of considerable importance in establishing an early diagnosis of the more serious complications of pregnancy.

Folin[1] in 1917, in an analysis of 100 cases, reported that the nonprotein nitrogen is seldom over 30 mg. per 100 c.c. of blood and that the urea nitrogen represents from 20 to 35 per cent of the nonprotein nitrogen. These findings were corroborated by Caldwell and Lyle[2] in 1921.

Slemons,[3] a year later, reported that when pregnancy is complicated by preeclamptic toxemia, the nonprotein nitrogen is normal and is frequently increased as soon as convulsions occur.

In 1921, Killian and Sherwin[4] reported low values for nonprotein nitrogen and urea nitrogen in normal pregnancy, the urea nitrogen constituting about 44 per cent of the non-protein nitrogen. They found no variation in the uric acid, creatinin, chloride, or sugar concentration of the blood of normal pregnant women as compared to that of nonpregnant women. In nephritic toxemia they found an increase in nonprotein nitrogen of which 50 per cent was in the form of urea nitrogen. They also report a definite increase in uric acid in this condition.

In 1924, Stander[5] reported that in normal pregnancy, the nonprotein nitrogen, as well as the urea nitrogen, is less than in the nonpregnant woman, the average being 28 and 12.48 mg. per 100 c.c. of blood respectively. The uric acid content is about the same as in the nonpregnant woman. The nonprotein nitrogen is increased in nephritic toxemia and the uric acid content of the blood is definitely elevated in all three types of toxemia, nephritic, preeclamptic and eclamptic.

Stander,[6] in 1929, reported that in the majority of cases of eclampsia, there is a tendency toward hyperglycemia and that following the convulsions there is a slight rise in blood sugar.

Titus,[7] in 1929, contrary to the findings of Stander, reported wide fluctuations in blood sugar values during eclampsia and noted that the convulsions are almost invariably preceded by a sharp fall in blood sugar.

It is of interest to note that most of these investigators concerned themselves chiefly with the nitrogenous constituents of the blood using different groups of cases for the different periods of pregnancy without following these changes in the same individual throughout the entire period of gestation. The present investigation was, therefore, undertaken to determine the changes in nonprotein nitrogen, urea nitrogen, creatinin, uric acid, sugar and chloride content of the blood throughout the entire period of gestation in the same individual.

With this in view, a study was made of ten cases of normal pregnancy, twenty cases of preeclamptic toxemia, five cases of eclampsia and five

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cases of nephritic toxemia, and the results were compared with a similar analysis of ten cases of normal nonpregnant women used as controls. Examinations were made upon patients from clinics of the Illinois Research and Cook County Hospitals. In the cases of normal pregnancy, blood examinations were made at intervals of 3, 5, 7, 8 and 9 months and first, third, fifth and ninth day puerperium and at six weeks after delivery. In the cases of preeclamptic toxemia, eclampsia and nephritic toxemia, two readings were taken before delivery and the same number of readings after delivery as for normal cases.

METHODS

In all cases, the blood samples were taken in the morning before breakfast. Potassium oxalate was used as an anticoagulant. The nonprotein nitrogen was determined by Koch-McMeekin's method,[8] urea nitrogen by Marshall's modified method, sugar[9] and uric acid[10] by Folin's method, creatinin by Folin and Denis'[11] method, and chlorides by Whitehorn's method.[12]

ANALYSIS OF RESULTS

Referring to Table I, which includes the average for the series of ten cases of normal pregnancy, it can be seen that the nonprotein nitrogen increases as pregnancy advances from 24 in the third month to 35.27 in the ninth month. The urea nitrogen also increases from 8.73 to 14.71 during that same period. Uric acid increases from 1.96 in the third

TABLE I. AVERAGE FOR SERIES OF NORMAL PREGNANCIES

DURATION OF PREGNANCY	N.P.N.	UREA N.	CREATININ	URIC ACID	SUGAR	CHLORIDES
3 months	24.434	8.7364	1.128	1.962	84.285	449.9
5 months	28.101	10.4844	1.189	2.382	79.615	447.5
7 months	31.82	10.04312	1.161	3.26	75.88	459.6
8 months	33.93	14.2377	1.16	3.62	69.82	454.8
9 months	35.27	14.71	1.194	4.15	70.47	444.8
1st day p.p.	29.54	14.17	1.28	3.04	79.46	450.4
3rd day p.p.	29.42	15.364	1.23	3.06	82.23	459.4
5th day p.p.	29.72	14.66	1.24	2.83	88.68	456.0
9th day p.p.	32.29	16.31	1.15	3.05	91.61	456.2
6 weeks	31.397	15.395	1.339	2.43	95.58	461.13

month to 4.15 in the ninth month, the latter figure representing a slight increase over that found in normal nonpregnant women. Creatinin and chlorides do not show any variation. Sugar decreases with the advancement of pregnancy from 84.2 in the third month to 70.47 in the ninth month.

Table II shows that in preeclamptic toxemia the nonprotein nitrogen varies from 21.69 to 33.97, the average being 29.39. The urea nitrogen was found to vary from 8.85 to 26.56 with an average of 16.06. The averages for uric acid and sugar were 3.23 and 78.41, respectively. It is,

therefore, seen that the findings in preeclamptic toxemia do not differ to any appreciable degree from those found in normal pregnancy.   It is furthermore significant that these figures returned to normal six weeks after delivery.

The figures obtained in eclampsia and nephritic toxemia are formulated in Table III.   In the former, the nonprotein nitrogen varied from

TABLE II.   PREECLAMPTIC TOXEMIA

CASE NO.	N.P.N.	UREA N.	CREATININ	URIC ACID	SUGAR	CHLORIDES	REMARKS
6	27.07	17.242	.86	2.50	82.78	418.5	
9	28.35	14.445	1.18	2.30	79.49	418.72	One kidney present Porro Cesarean
10	30.00	8.854	1.18	3.61	75.47	449.24	
39	29.51	17.242	1.42	1.90	72.30	470	Cesarean Section
18	30.00	16.776	1.69	3.63	75.01	462	
19	28.57	8.854	1.40	2.22	81.63	478	Normal delivery
20	25.53	9.320	1.30	1.76	72.30	466	Normal delivery
21	29.04	13.866	1.05	4.06	97.56	440	Porro Cesarean
23	33.97		1.43	2.70	71.02	450	Edema B.P. 200/130 Normal delivery
25	23.38	6.8036	1.07	2.18	89.56	466	B.P. 170/120 Edema
28	33.65	26.562	1.42	4.61	70.59	466	Normal delivery
29	37.90	20.6904	1.16	4.18	78.95	440	Normal delivery
31	21.69	17.8012	1.80	2.35	98.37	450	B.P. 166/100
32	25.35	17.708	1.28	2.59	83.33	470	Mitral Regurg.
33	25.90	20.504	1.01	2.62	76.92	456	
34	33.65	24.232	1.28	3.13	64.18	450	B.P. 150/90
35	42.30	23.30	1.25	5.21	87.60	450	Cesarean Section
36	31.86	15.378	1.69	7.20	73.17	468	
37	23.84	13.514	1.40	3.05	66.66	452	B.P. 170/110 Forceps delivery
38	26.43	12.116	1.63	2.97	71.42	442	Normal delivery
Average	29.399	16.06		3.238	78.415		

TABLE III.   NEPHRITIC TOXEMIA

CASE NO.	N.P.N.	UREA N.	CREATININ	URIC ACID	SUGAR	CHLORIDES	REMARKS
27	45.59	26.8416	1.13	6.43	78.43	470	Cesarean Section
16	67.25	43.804	1.34	10.44	117.64	476	Macerated Fetus
7	28.57	8.481	1.28	2.60	85.72	503.78	Albuminuric Retinitis
22	43.38	19.1992	1.50	8.36	75.47	466	
30	34.62	18.64	1.69	3.05	118.83	464	Luetic Aortitis
Average	43.88	23.39		6.17	95.21		
			ECLAMPSIA				
			(Following Convulsion)				
26	33.33	17.1488	1.25	3.69	179.21	462	
24	38.70	15.611	1.40	4.61	103.46	454	3 convulsions Macerated Fetus
17	40.92	19.106	1.40	5.45	184.35	460	Forceps Delivery
40	64.30	34.62	2.19	10.21	148.10	468	Cesarean Section
			(Before Convulsion)				
14	31.86	12.42	1.40	3.75	66.31	434.2	Forceps Delivery
Average	41.82	19.781		5.54	153.78 66.31		

Average for Normal Pregnancies

Fig. 1.

Six Weeks after Delivery
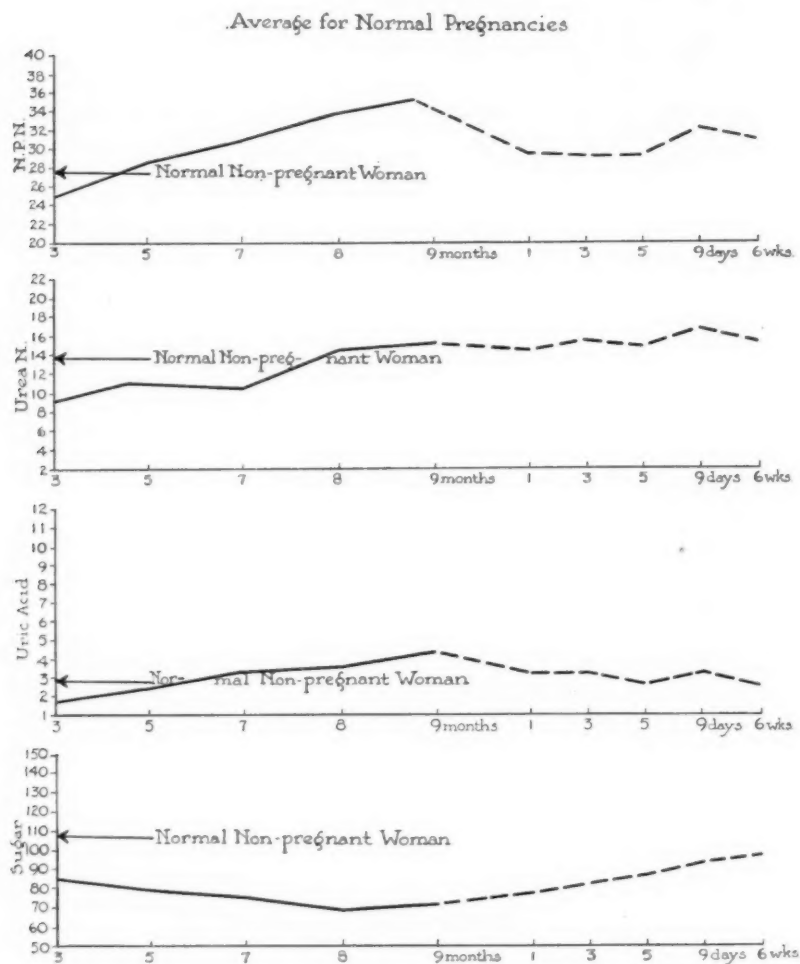
Fig. 2.

31.86 to 64.30 with an average of 41.82.   Urea nitrogen varied from 12.42 to 34.62 with an average of 19.78 and the average for uric acid was 5.54. It is therefore seen that the nitrogenous elements in this condition shows an appreciable rise over the normal.   A more striking difference was found in the case of sugar which rose from 66.31 before the convulsions occurred to that of 153.78 following the convulsions.   Here, as in the case of preeclamptic toxemia, the blood findings were normal six weeks after delivery.

In nephritic toxemia, the nitrogenous elements show a greater increase than that found in all the above conditions, the nonprotein nitrogen, urea
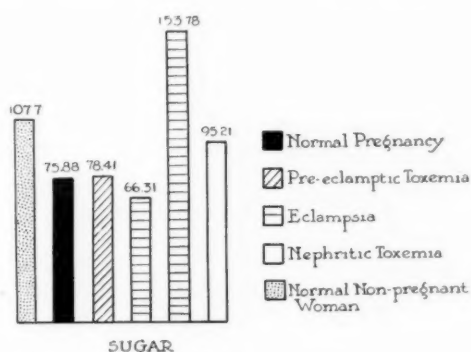
Fig. 3.
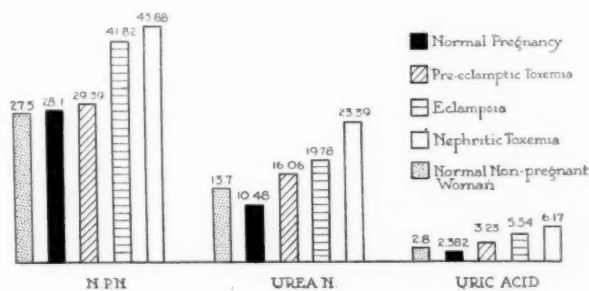
Six Weeks after Delivery

SUGAR

Fig. 5.

Fig. 4.
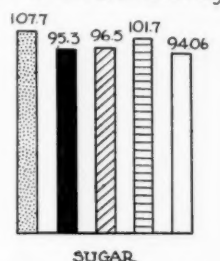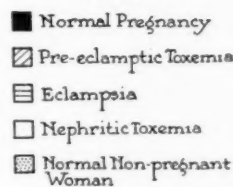
nitrogen and uric acid averages being 43.88, 23.39 and 6.17 respectively. The sugar showed little variation from the normal nonpregnant cases, the average being 95.21.   But the most striking and significant difference between this condition and eclampsia lies in the fact that here the nitrogenous constituents show practically no tendency to return to normal even at the end of six weeks.

COMMENT

It was originally hoped that the results of this investigation might prove of diagnostic import in the complications of pregnancy, but inasmuch as the clinical symptoms appear before any changes in the chem-

istry are manifested, the latter offer little information as to the diagnosis; however, they play some rôle in the prognosis of these conditions, since there is an increase in the uric acid content of the blood in preeclamptic toxemia, eclampsia and nephritic toxemia and the increase in each condition is proportional to the severity of the disease.

Eclampsia is differentiated from nephritic toxemia by the fact that the increase in the nitrogenous constituents in the latter does not return to normal after six weeks. With reference to the sugar content in eclampsia, the results of this investigation, in a way, corroborate the work of Titus and also of Stander inasmuch as there was hypoglycemia immediately preceding a convulsion and a sharp rise in the sugar content immediately following a convulsion. It might be casually added that the beneficial results of glucose therapy in eclampsia obtained by Titus may justify his contention that the hypoglycemia is the underlying disturbance in that condition.

CONCLUSIONS

In summarizing the salient points of this investigation it is noted that

1. There is an increase in the nonprotein nitrogen from 24 in the third month to 35.27 in the ninth month.

2. Uric acid shows a slight increase during the ninth month of pregnancy.

3. The sugar content of the blood is diminished from 84.2 in the third month to 70.47 in the ninth month.

4. In preeclamptic toxemia, the nonprotein nitrogen, urea nitrogen, and uric acid show a slight increase over that found in normal pregnancy with a return to normal in six weeks.

5. In eclampsia, the nonprotein nitrogen, urea nitrogen, and uric acid show a greater increase than that found in preeclamptic toxemia with a similar return to normal.

6. In nephritic toxemia, the nitrogenous constituents show a more marked increase than that found in any of the conditions here considered differing from eclampsia in that they do not return to normal even at the end of six weeks after delivery.

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3508 WEST ROOSEVELT ROAD

AN ANALYTIC STUDY OF 1,000 CASES OF CESAREAN SECTION

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CESAREAN section is apparently on the increase; the reasons for this are numerous. Improved technic and a more thorough knowledge of the conditions under which a cesarean may be performed have greatly reduced the initial risk. Today, operation is preferred to the hazard of fetal injury or severe maternal damage. Better obstetric teaching has resulted in a more general recognition of cephalopelvic disproportion. On the other hand, cesarean sections are performed in the presence of real or only apparent dystocia, in preference to delivery by some more legitimate procedure. Reduction in the mortality rate in the last decade is lessening the hazard in the minds of physicians, and this, we believe, is increasing the incidence of cesarean operation beyond the rational limits of scientific obstetrics. There is, moreover, the ever-present problem of the reoperative cesarean in those who have once been delivered by this route.

Notwithstanding many improvements, the mortality in cesarean section is still high. This is especially true in certain sections of the country and among certain groups of operators. The classical operation has always been and is still the most popular procedure. It is the oldest, the simplest in point of technic and is the only type attempted by many operators. Other approaches, such as the extraperitoneal cesarean, the Porro, the Portes operation, are performed only under unusual conditions, and, with the possible but improbable exception of the extraperitoneal, none are likely to become standard procedures.

The present paper is based upon a complete study of 1,000 cases drawn from a consecutive unselected series of 1,257 performed by all operators at the Robinson Memorial* from January 1, 1911, to February 1, 1931. The deletion of 257 cases in the series was due chiefly to the inaccessibility of certain of the earlier records and to those cases where the individual operation was of some special type, such as vaginal section, the total number of which was too few to warrant statistical comparison. For purpose of contrast we have divided the whole period into two parts; namely, 1911 to 1919, inclusive, and from 1920 to 1931. This division enables us to compare two approximately equal periods, during the first of which the classical operation was practically the only operation performed, while in the second the low cervical operation was first instituted and has gradually superceded the old procedure.

During this period (January 1, 1911, to February 1, 1931) there were a total number of 31,613 confinements. The out-patient deliveries, num-

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*The maternity department of the Massachusetts Memorial Hospitals.

bering 3,038 are obviously included in our list because all operative cases encountered in the district are sent into the house for delivery. The statistical data are given in Table I.

TABLE I. SUMMARY OF TOTAL CONFINEMENTS AND MATERNAL DEATHS

| YEAR | CONFINEMENTS | | | MATERNAL DEATHS | |
	House	Out-patient	Total	Number	Per Cent
1911-1915	4449	1163	5612		Omitted as data incomplete
1916-1919	6409	729	7138	82	0.90% to 1.33% Av. = 1.15%
1920-1931*	17717	1146	18863	190	0.39% to 1.54% Av. = 1.01% Av. 1927-31 = 0.97%
Total	28575	3038	31613	272	Av. 1916-31 = 1.05%

*Up to Feb. 1, 1931.

But few comments are necessary. For the period containing dependable records maternal deaths fluctuate within narrow limits about 1 per cent, the number being 272 in a total number of confinements of 26,001, or 1.05 per cent.

A primary analysis of the fundamental data as relating to the cesarean operations can best be presented in graphic form (Chart 1).
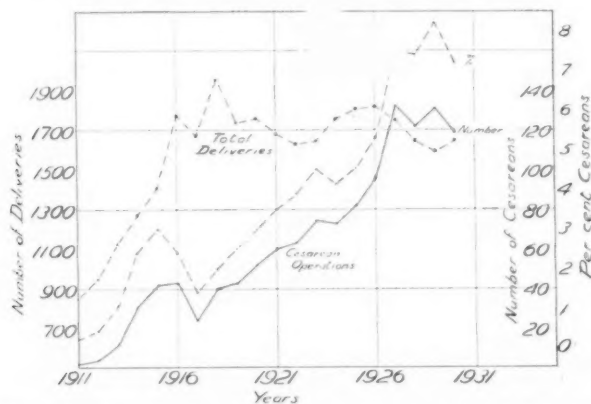

Chart 1.—Relation of cesarean section to total deliveries.

During the first portion of the period, the number of deliveries shows a steady increase, but has remained at a fairly constant level, determined by the hospital capacity, since 1916. The cesarean operations have increased steadily in number from 2 in 1911 to 131 in 1929. The figures for 1931 are omitted, since only January is considered, but 12 cesareans were performed in 130 deliveries, or 9.2 per cent. The influence of the low operation is manifest both in the absolute increase and in the more pronounced upward trend of the percentage curve in the years following its introduction.

Of the 1,000 cases, 624 were abdominal sections; this includes a few transperitoneal as well as the usual extraperitoneal type of procedure

and one case of abdominal pregnancy; the remaining 376 were laparo-
trachelotomies. The Porro operation was performed seven times. Several
attempts were made to induce labor in the single case of abdominal
pregnancy, and the radiogram showed a fetus apparently in utero, at full
term, with the head at the pelvic brim.*

Two hundred seventy-seven of the patients had had at least one
previous cesarean. The maternal mortality in the cases having cesarean
section was 54 with a fetal mortality of 89. While the death rate of the
infants seems unduly high, it must be remembered that many of the
babies were premature and in one instance, under the age of viability,
the section being performed in the interest of the mother. This will be
considered in detail in a subsequent table.

The maternal mortality and the analysis of the results of the two
types of cesarean operation can be presented most compactly in tabular
form.

TABLE II. MATERNAL MORTALITY STATISTICS

YEAR	TOTAL CESAREAN OPERATIONS	CLASSICAL OPERATIONS			LAPAROTRACHELOTOMIES		
		SURVIVED	DIED	TOTAL	SURVIVED	DIED	TOTAL
1911	2	2	0	2			
1912	1	1	0	1			
1913	15	13	2	15			
1914	31	26	3	29	Operation		
1915	42	37	2	39	not performed		
1916	43	37	5	42	during this		
1917	24	16		20	period.		
1918	40	29		29			
1919	43	31		37			
1920	52	41	2**	43	4	0	4
1921	60	37	2	39	2	0	2
1922	63	52	5	57	1	0	1
1923	74	65	7	72	9	1	10
1924	73	43	3	46	6	0	6
1925	82	40	1	41	22	0	22
1926	96	27	1	28	34	0	34
1927	132	35	3	38	74	1	75
1928	122	4	0	4	43	0	43
1929	131	14	1	15	79	1	80
1930	119	24	2	26	86	2	88
1931*	12	1	0	1	11	0	11
Totals	1257	575	49	624	371	5	376

*Only month of January.
**Includes case of abdominal pregnancy.

The discrepancies in the table between the record of total cesareans
and the sum of the classical and laparotrachelotomy cases are due
primarily to the incompleteness of the records noted in the body of the
paper. A second and minor factor comes from the omission of a number
of operative deliveries by routes other than the two considered in this
paper.

Inspection of these data shows some significant relationships. From

*The surgeon's quotation is as follows: "A dead baby was found in the
abdominal cavity with the head lying in the pelvic cavity. The uterus was found
twice normal size and contained a fibroid projecting from the left cornu—the
placenta was attached to the mesentery—the cord was tied and the baby ex-
tracted—the fibroid removed and the placenta left in the abdominal cavity."

1911 to 1919, inclusive, there were 214 abdominal sections with a maternal mortality of 22, or 10.2 per cent. During the next period, 1920-1931, the classical operation was performed on 409 patients with a total of 26* maternal deaths, or 6.4 per cent. The first laparotrachelotomy was performed in 1920, and during the period since that time a total of 376 "two flap" operations have been performed. This series shows only 5 maternal deaths, or 1.33 per cent. These figures obviously contrast most favorably with those from the series of classical operations.

In comparing the end-results of the two methods of approach, a series of other considerations are worthy of attention. Added factors before, during, and after delivery all may play some part in determining the outcome and a few of these may be briefly reviewed.

TRIAL LABOR

Sections were performed on 285 cases, or approximately 25 per cent, which were known to have had trial labors. The extent of labor specified in hours varied from one to 120. The greatest number of cases (60) had from six to ten hours' labor, although almost as many (52) had five hours or less. There was a total of 20 deaths, a percentage of 7.07 per cent. Eighty-five cases in the series had labor terminated by classical section, while 200 had laparotrachelotomies. Of the deaths, 17 occurred in the brief series of 85 patients with classical operations (20.0 per cent) while in the much larger group with the low operation, only 3, or 1.5 per cent died.

ADDITIONAL OPERATIONS

About one-third of the entire series (327) had some other operation performed at the time of the section. Of minor statistical import are records of one posterior gastroenterostomy, two umbilical herniotomies,

TABLE III. INDICATIONS FOR STERILIZATION

CONDITION	NUMBER	TOTAL
Previous Cesarean (one to four)	120	120
Earlier Pregnancies (three to ten)	23	
Mental	2	
Cardiac	23	
Constitutional	17	
Structural	16	
Toxemias	9	
Imbecile Children	2	92
Cause not given		41
	Total	253

five myomectomies and seven (Porro) hysterectomies. Fifty-nine of the patients had appendectomies with a record of one maternal death in the group. By far the most common operation was that of sterilization, 253 of the patients, or 77 per cent of this group, being manipulated for this purpose. A record of earlier cesareans was the indication of most frequent report for sterilizing operations but certain others ap-

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*Excluding case of abdominal pregnancy.

peared in significant numbers. A summary of reported causes is given in Table III.

FETAL POSITION

This was recorded in about three-fourths of the cases and the principal divisions are recorded as a matter of possible interest.

TABLE IV.

POSITION	NUMBER	
R.O.P.	239	
L.O.P.	94	
L.O.A.	209	
R.O.A.	103	
Breech	92	
Posterior (unclass.)	10	
Transverse	17	
Face	4	768
Not specified		232
	Total	1000

A fact of interest relative to fetal positions may be noted. Out of 768 cases classified almost one-half had posterior positions. Probably this single factor was important in helping to determine the type of delivery in such cases.

DRAINAGE

This topic is included because of interest during the first period in the efficacy of drains and saline flushes. There were 17 deaths in 127 cases. During the second period there was no record of saline flushing of the abdominal cavity. With this latter procedure there were 8 maternal deaths in 68 cases, a mortality of 11.7 per cent. The use of drains was even less successful, 59 cases being reported with nine deaths, or 15.3 per cent mortality.

MORBIDITY

For purposes of emphasis we have considered every elevation of temperature over 100° F. during the patient's stay in the hospital as morbidity, even though it be recorded but once on the chart. This is, of course, an unwarrantably rigorous standard for any general con-

TABLE V.

TEMPERATURE	CLASSICAL OPERATION			LAPAROTRACHELOTOMIES		
	No.	%		No.	%	
No elevation	42	6.7	27.2%	245	65.2	96.3%
100 — 101	128	20.5		117	31.1	
101 — 102	225	36.1		12	3.2	
102 — 102.5	144	23.1	36.7%			
102.5 — 103	44	7.0		2	0.5	
103 — 106	41	6.6				

sideration. In the present instance, in which comparison between the two operative routes is the thesis, the relative values are so strikingly differentiated that this rigorous standard has seemed admissible. For purpose of comparison the morbidity has been classified separately and the data are given in Table V.

Note that out of a total of 624 classical sections (includes case of abdominal pregnancy) only 42 cases had no elevation in temperature, or about 6.7 per cent. Compare this with the laparotrachelotomies, which numbered 376 and among which 245 had no elevation in temperature, or 65.2 per cent. This is a tremendous difference in the morbidity rate even though approximately four times as many laparotrachelotomies had a trial labor. A still more striking comparison is found in the relative figures of 229 classical operations after which there resulted temperatures of 102° and higher as compared with only two cases in a similar group among the laparotrachelotomies.

The causative factors for morbidity as reported, included 35 different conditions. Wound infections (78), other infections (79), and disorders of the respiratory (77), cardiorenal (88), gastrointestinal (11) and circulatory system (32) accounted for practically all of the 370 cases with complete records. The records of the remaining 343 assigned no specific reason and in the majority of cases morbidity was no more than a natural and transitory result of the surgical manipulation.

Wound infections constituted the largest single group. Among other infections those of the respiratory system 20 cases of bronchopneumonia, 14 of influenza, and 10 of pleurisy are the most significant. There were 58 cases of pyelitis with 15 of pyelonephritis, and 13 of chronic nephritis. Twenty-five abscesses were reported, while inflammatory processes of the endometrium accounted for 17 cases. There were 14 cases of peritonitis, 14 of mastitis, and 6 of phlebitis. In the circulatory group there were 6 patients with septicemia, secondary anemia and sapremia being present in the remainder.

INDICATIONS

The classification of indications is somewhat difficult, in view of the wide variety of reasons which have been given. Since 1920, the major portion of the operations have been decided and performed by the obstetricians on the staff; during this period the accepted conditions have been practically limited to (a) cephalopelvic disproportions, (b) earlier cesareans, (c) antepartum bleeding, and (d) toxemias. Generally speaking, the classification of indications as outlined by Holland[1] and Gordon[2] have been adopted with such modifications as are explained under the proper headings. Each will be briefly discussed.

1. Contracted Pelvis.—Under this indication a total of 347 operations were performed, with a maternal mortality of 12, or 3.45 per cent. This group includes one case of abdominal pregnancy. Only such records are included in this group as gave contracted pelvis as an indication for

section; others which may be listed as "previous cesarean" may also have had contracted pelvis.

Classical sections were performed on 214 patients, or 61.7 per cent as compared with 133 patients which had laparotrachelotomies, or 38.3 per cent. The maternal mortality is very striking. Ten women (4.67 per cent) died following classical sections as compared with 2 deaths (1.50 per cent) following the low cervical operation. The baby deaths require no comment beyond the slightly lower mortality in the two flap operation (3.3 per cent and 2.3 per cent).

2. *Toxemias.*—This is a difficult group for distinct and separate subdivision. Williams lists the following: (a) pernicious vomiting, (b) acute yellow atrophy of liver, (c) nephritic toxemia, (d) preeclamptic, (e) eclamptic, (f) presumable toxemia. In our group, the first period of our report (1911-1920), nephritic toxemias as well as presumable toxemias were common indications for section; in this same period cesareans were performed more frequently on cases of eclampsia, where the patient had convulsions before delivery.

The 78 cases which comprise this group, may be divided as follows: (A) Eclampsia, 8 cases; (B) preeclampsia, 14 cases; (C) nephritic toxemias, 56 cases.

A. Eclampsia.—In this group 7 cases had classical sections with 3 deaths and 1, a successful laparotrachelotomy. The maternal mortality is indeed high. The fetal mortality was 50 per cent; prematurity, however, accounted for half of this mortality.

B. Preeclampsia.—These 14 cases were equally divided, the single death falling in the classical series. The fetal mortality was confined to the group with laparotrachelotomies with one full-term and two premature deliveries.

C. Nephritic Toxemias.—This group has a total of 56 cases. Forty-five cases had classical sections, seven of which, or 15.6 per cent died. Ten cases had laparotrachelotomies with one death. In this group there were included two cases of albuminuria, without other toxemic symptoms, three cases of acute nephritis, one case of uremia with convulsions, and one case of hypertension. There were 5 fetal deaths, one full-term and four premature deliveries all in the classical group.

3. *Antepartum Hemorrhage.*—Serious antepartum hemorrhage is a very grave complication of pregnancy. The trend today is to turn without hesitation to cesarean section for this complication.

Accidental hemorrhage and placenta previa comprise the group. There were ten cases of the former with one maternal death and 43 cases of the latter with 3 deaths. All of these deaths were patients sent into the hospital *in extremis*, and on whom attempts at delivery per vaginam had been made before admission.

The question of doing cesarean sections in infected cases of placenta previa has been discussed many times. Most writers feel that the operation should be confined to clean cases. We feel that with the advent

of the laparotrachelotomy we should not fear to perform a section in infected cases also. Uterine wounds are the source of spreading infection to the peritoneal cavity, but with the laparotrachelotomy the chances are much less than with the classical section.

(a) Placenta Previa.—Forty-three cases comprise this group. The 3 deaths all occurred in the classical group of 31 cases; in addition there were 12 survivals with the low operation. The total maternal mortality was 6.9 per cent. There were no deaths in cases which were admitted to the hospital without previous attempt at delivery. Of the 12 cases which had laparotrachelotomies, 2 cases were frankly infected and it is interesting to note that both survived. We feel that the low cervical operation is the elective choice in such cases.

The fetal mortality was 20.5 per cent. This includes one nonviable fetus and 5 prematures. Deducting these 6 deaths, the net fetal mortality was 6.8 per cent, all in the classical group.

(b) Accidental Hemorrhage.—In all instances of fetal mortality (60 per cent) the heart sounds were not obtained before operation. In the one case of maternal death the patient was admitted into the hospital *in extremis.* The 2 cases of laparotrachelotomies were infected before admission to the hospital: with this fact the choice of cesarean operation was the newer method. Again it is interesting to note that both cases made uneventful recoveries.

4. Heart Disease.—It is at this point that we make a modification in the grouping of indications, as outlined by Holland and by Gordon in their articles using separate classifications for heart disease and for previous cesareans.

There was a total of 24 cases of heart disease. The majority of these cases (18) were primiparae. Classical sections were performed in 22 cases with four maternal deaths. Two cases had laparotrachelotomies with no fatality. The total maternal mortality was 16.6 per cent. The fetal mortality was confined to 1 full-time and 3 premature infants in the classical group.

5. Previous Cesareans.—Under this indication are included four cases of ruptured uterus. There was a total of 277 previous cesareans.

> 176 had one previous cesarean
> 69 had two previous cesareans
> 31 had three previous cesareans
> 1 had four previous cesareans

There were seven maternal deaths among 156 classical sections performed, a percentage of 4.5. There were no maternal deaths among 121 laparotrachelotomies. The fetal mortality statistics show 17 full-term and 7 premature infants in the classical group and three each in the low operation series.

6. Unengaged Head.—Fifty-four cases comprise this group. Probably a large number of these cases could be listed under the indication

of contracted pelvis, but unengaged head was given as indication. The 3 maternal deaths were all in the 34 patients operated upon by the classical route; the remaining 20 patients having low operations all survived. Only one full-term and one premature infant died in the first series; none in the second.

7. *Pelvic Pathology.*—This group includes the cases which had gynecologic conditions as indications for operation: thus the existing pathology was the disturbing factor either before or during labor.

Twenty-six cases had had previous operations, which were divided as follows: five cases, an anterior and posterior colporrhaphy with amputation of the cervix; twelve cases, a uterine suspension; two, a repair of the cervix; one, lysis of adhesions; three, previous abdominal operations; and three perineorrhaphies.

Twelve cases of fibromyomata uteri had classical sections without maternal or fetal mortality.

One case of dermoid cyst had a classical section performed, without maternal or fetal mortality.

There were two cases of umbilical hernia, one of which had a classical operation while the other had the newer procedure. Both were successful.

8. *Miscellaneous Conditions.*—This classification is obviously a difficult one. The plan adopted is similar in some respects to that of Gordon. The data can be presented most compactly in tabular form (Table VI).

TABLE VI.

CONDITION	MATERNAL				FETAL DEATHS			
	Class.		L.– T.		Class.		L. – T.	
	No.	Died	No.	Died	Term	Prem.	Term	Prem.
Contraction ring	1	0	0	0	0	0	0	0
Dystocia: rigidity of cervix	5	1	5	0	0	0	0	0
Congenital malformations	2	0	1	0	0	0	0	0
Grave maternal diseases	7	0	4	0	1	0	0	0
The fetus	16	2	3	0	2	0	0	0
Rupture of the uterus	3	3	0	0	2	1	0	0
Accidents in prenatal period	1	0	1	0	0	0	0	0
Miscellaneous	35	2	42	2	4	1	0	1
Total	70	8	56	2	9	2	0	1

TABLE VII. SUMMARY

MAJOR CONDITION	PERCENTAGE OF GROUP	MORTALITY PERCENTAGE	
		CLASSICAL	LAPAROTRACHELOTOMIES
Contracted Pelvis	34.7	4.7	1.5
Toxemia	7.8	18.6	5.3
Hemorrhage	5.3	10.3	0
Heart	2.4	18.1	0
Previous Cesarean	27.7	4.5	0
Head Presentation	5.4	8.8	0
Pelvic Pathology	4.1	6.9	0
Miscellaneous	12.6	11.4	3.6
Total Mortality		7.81	1.33

DISCUSSION

The main facts elicited in this analysis are presented in tabular form (Table VII).

Contracted pelvis, the indication in over one-third of the entire group, is a structural condition of local import only as determining operation. True, it may have arisen through earlier metabolic disturbance, but any such influence cannot be regarded as immediately operative in a woman who is completing a normal pregnancy. The comparative data are the more significant in this condition because of its character; mortality is over three times as great in the classical as in the newer procedure.

Toxemias are general systemic conditions and in this group the laparotrachelotomy records its highest mortality. These deaths are to be ascribed more to the grave disease state than to the operative hazard. Again it is significant that the older operation shows more than three times as many deaths. This is susceptible of interpretation as the effect of the operation superimposed upon the constitutional state.

In the highly varied group constituting one-eighth of the series, again we find a greatly augmented mortality by the older route, the ratio being substantially the same as in the two previous groups. The lack of uniformity of the underlying pathology in this scatter of cases makes comparison somewhat less authoritative; none the less the trend is unmistakable.

To complete the case for the laparotrachelotomy it is only necessary to consider the other indicating factors, nearly half of the total series, in each group of which, the older method records an appreciable mortality while the newer approach records not a single death. While the basic figures are the same as in the preceding portion of the paper, the consistency of the superiority is impressive in the more detailed approach.

SUMMARY

Analysis of 1,000 cases of cesarean section in which either the classical operation or laparotrachelotomy was performed shows that the newer procedure is greatly superior in its lower mortality (1:5), its lessened unfavorable response to trial labor (1:13), and the much lower frequency of postoperative morbidity (1:10). Where anatomic consideration or time factor does not necessitate reversion to the classical procedure, laparotrachelotomy is clearly the method of election.

REFERENCES

(1) *Holland, E.:* J. Obst. & Gynec. Brit. Emp. **28**: 358, 1921.   (2) *Gordon, C. A.:* AM. J. OBST. & GYNEC. **16**: 307, 1928.

587 BEACON STREET.

THE RELATION OF AMENORRHEA ACCOMPANIED BY GENITAL HYPOPLASIA TO THE FOLLICULAR HORMONE IN THE URINE*

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THE treatment of amenorrhea especially when accompanied by some degree of genital hypoplasia has, in our hands, rarely yielded any cures. The treatment consisted of the injection of one cubic centimeter of Sistomensin† once or twice a week, and the administration by mouth of 6 c.c. per day of a raw extract of the whole ovary,‡ as well as 6 c.c. per day of a raw extract of anterior pituitary.

In addition, almost all of the patients received a weekly intramuscular injection of 10 to 20 c.c. of blood§ taken from patients in the last half of pregnancy. In many cases the treatment was persisted in for more than a year without any results, in an occasional case a slight uterine hemorrhage of a day's duration occurred which symptomatically did not resemble a true menstrual period.

It has been determined by other investigators[1, 3, 4] and by us[2] that there is a constant excretion of small amounts of follicular hormone in the urine of all normal women throughout their sex life, and often into the menopause.[2, 4] (Tables I and II.) The amounts excreted vary from several mouse units (M.U.) to several rat units (R.U.) per liter of urine, one R.U. being equivalent to 6 to 12 M.U. It occurred to us that our cases of amenorrhea may already be excreting follicular hormone in the urine. To demonstrate this, twenty-four-hour samples of urine were obtained from these patients and the follicular hormone extracted according to the method of Clarke and Kurzrok.[5] Where the patients had been treated with ovarian extracts, a period of a month was allowed to elapse without treatment before the urine was collected.

METHOD FOR EXTRACTION AND ASSAY OF FOLLICULAR HORMONE IN A TWENTY-FOUR-HOUR URINE SPECIMEN

The twenty-four-hour urine specimen is measured and 700 c.c. placed in a one-liter flat-bottomed flask (A) (Fig. 1). This is made weakly acid with acetic acid. The hormone is more easily extracted from an acid solution. The urine is then saturated with sodium chloride which decreases the solubility of ethyl acetate in the urine. The treated urine is then covered with ethyl acetate halfway up to neck of the
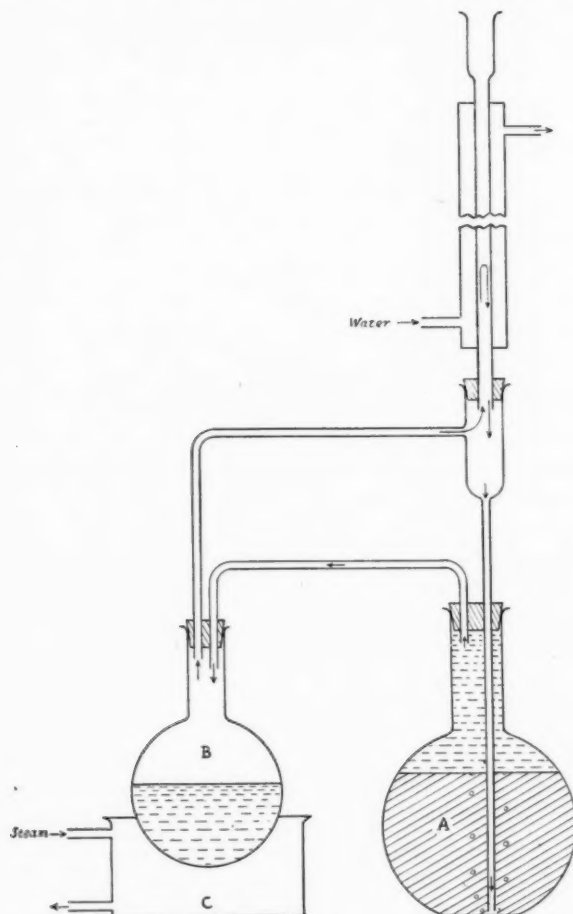

Fig. 1.—The follicular hormone extraction apparatus. The distance between the upper and lower side arms should be 3 to 4 inches. The condenser should be long, as the ethyl acetate is fairly volatile.

flask and the flask connected as shown in Fig. 1. The second flask (B) of 300 c.c. capacity is filled with 250 c.c. of ethyl acetate. The steam bath (C) is turned on and the ethyl acetate distills over through the upper side arm, is condensed and drops to the bottom of flask A from which it returns through the lower side arm to flask B. The drops of ethyl acetate in passing upwards through the urine extract the hormone. This provides continuous extraction with pure ethyl acetate. The extraction is continued for twenty-four hours. It is automatic and does not need watching. The extracted urine is then discarded, and the ethyl acetate extract, which contains the hormone, is concentrated by vacuum distillation in the apparatus il-

lustrated in Fig. 2. The distilling flask (*A*), 300 c.c., is filled one-third full with the ethyl acetate extract and connected with the condenser (*B*), a receiving flask (*C*), a second receiving flask (*D*), a trap (*E*) and finally an aspirator type suction pump (*F*). After the distilling flask has been heated in a steam bath, the suction is turned on. The remaining extract is allowed to drop into flask (*A*) through the thistle tube (*G*), which is provided with a stopcock, at about the same rate as the ethyl acetate distills over. When all the extract is finally added, it is concentrated further to about 30 or 40 c.c. and the 10 c.c. of olive oil is slowly admitted through the thistle tube as the distillation progresses. The distillation is continued until all the ethyl acetate has been removed. If bumping occurs, the suction should be reduced with the screw clamp at (*H*). The oil now contains the hormone originally present in the 700 c.c. of urine.
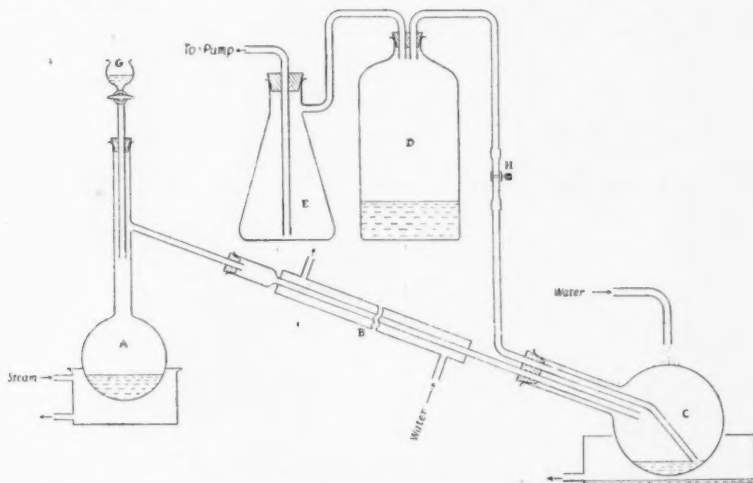

Fig. 2.—The concentration apparatus. The receiving flask (*D*) should be 3 to 5 liter capacity. It acts as a reservoir and is only emptied of ethyl acetate when full. Aside from removing and replacing the distilling flask, the apparatus need not be disconnected.

This 10 c.c. of oil, prepared as described above, is used for the biologic assay. Two groups of castrated rats are selected containing three animals in each group. They are injected with the oil, subcutaneously, in the back, at 9 A.M., and 5 P.M. of the first day, and 9 A.M. of the second day. Group 1 receives 0.5 c.c. of oil at each injection. Group 2 receives 0.25 c.c. of the oil at each injection. Vaginal smears are taken forty-eight, fifty-six, and seventy-two hours after first injection. A No. 13 dental spatula is very convenient for obtaining the vaginal secretion, which is then spread in a drop of saline on a glass slide. If no fewer than two animals of a group show the cornified cells characteristic of estrus, the injected material may be considered active. Mucus, leucocytes and epithelial cells must be absent to establish a positive result. The least amount of oil necessary to produce a positive smear is considered as containing one rat unit.

The hormone content of a liter of urine, expressed in terms of rat units, may be calculated from the following formula.

$$\frac{10}{y} \times \frac{1000}{700} = \text{Rat unit per liter of urine,}$$ when y equals the total amount of oil injected into a single rat from the group receiving the smallest amount necessary to produce positive smears.

For example: If Group 1 should have positive smears and Group 2 negative smears, then there would be 9 rat units per liter of urine, while if both Groups 1 and 2 showed positive smears, there would be at least 19 rat units present. Larger amounts of hormone may be determined by using smaller quantities of oil for injection, or by making the necessary dilutions. The calculations may also be made for the total

TABLE I. FOLLICULAR HORMONE IN THE URINE IN CASES OF AMENORRHEA PLUS GENITAL HYPOPLASIA

NAME	AGE	SYMPTOMS	CLINICAL DIAGNOSIS	QUANTITATIVE ESTIMATE OF FOLLICULAR HORMONE IN ONE LITER OF URINE	RESULTS OF TREATMENT
M. H.	17	Irregular periods Amenorrhea for five months	Genital hypoplasia	17 R. U.	None
J. B.	17	Amenorrhea 14 mo.	Genital hypoplasia	8 R. U.	Had scant flow after two months' treatment
S. H.	22	Amenorrhea 18 mo.	Genital hypoplasia Froehlich Syndrome	None on first test. 9 R. U. (later)	None
A. B.	21	Amenorrhea 18 mo.	Genital hypoplasia	8 R. U.	None
C. I.	24	Amenorrhea 2 years	Genital hypoplasia Masculine stigmata	15 R. U.	None
M. K.	43	Amenorrhea 1 year. No menopause symptoms. Some genital	Some genital atrophy	10 R. U.	None
I. M.	33	Amenorrhea 1 year	Genital hypoplasia	22 R. U.	None
M. K.	26	Irregular periods Amenorrhea 6 mo.	Gained fifty pounds. Basal Metabolism +40. Negative pelvis	13 R. U.	None
A. G.	23	Infrequent periods Amenorrhea 3 mo.	Gained 125 pounds in 4 yr. Basal Metabolism, 3. Froehlich Syndrome	23 R. U.	None
L. F.	36	Amenorrhea 4 mo., preceded by amenorrhea of 2 yr.	Carcinoma of adrenal cortex. Virilism	18 R. U.	None
R. D.	21	Irregular and scanty periods. Sterility	Genital hypoplasia Male stigmata	22 R. U.	None
S. H. II.	18	Irregular and scanty periods Amenorrhea 4 mo.	Genital hypoplasia Male stigmata	9 R. U.	None
E. P.	36	Amenorrhea 10 mo.	Genital hypoplasia	18 R. U.	None

amount of urine excreted in twenty-four hours by substituting this amount in the equation in place of 1000.

The results as demonstrated by Table I show that our patients with amenorrhea excreted considerable quantities of follicular hormone, in amounts ranging from 8 to 23 R.U. per liter. The average here is slightly higher than that obtained with normally menstruating women. Such being the case, we can gain no possible advantage by the further addition

TABLE II.   FOLLICULAR HORMONE IN THE URINE IN NORMAL AND OTHER CASES

NAME	AGE	SYMPTOMS	CLINICAL DIAGNOSIS	QUANTITATIVE ESTIMATE OF FOLLICULAR HORMONE IN ONE LITER OF URINE	RESULTS OF TREATMENT
R. W.	51*	Flushes, etc.	Menopause following x-ray radiation	15	No results from ovarian therapy
P. P.	30*	Very severe dysmenorrhea	Genital hypoplasia	21	No results from ovarian therapy
E. P.	32*	Flushes, sweats. etc.	Menopause following bilateral oophorectomy	0	Moderate relief from ovarian therapy
B. S.	29	None L. M. P.—4/17/31	Relaxed pelvic floor Tested, 5/14/31	11	
M. D.	31	None L. M. P.—5/18/31	Cystocele Test 5/14/31	11	
E. L.	32	None L. M. P.—4/25/31	Supravaginal hysterectomy on 1/30/31 Tested, 5/14/31	19	

*We are beginning to get the impression that only these cases of menopause are benefited by follicular hormone that are not excreting any hormone in the urine.

of 5 to 10 R.U. of follicular hormone per day. Our failure to produce a cure or even an improvement in the above cases proves the correctness of this viewpoint. The excretion of such relatively large quantities of hormone may mean that the production of the hormone is one factor and its utilization is quite another. Follicular hormone is probably not directly responsible for menstruation. The menstrual flow is to be regarded as a polyhormonal phenomenon in which the anterior pituitary and the corpus luteum hormones play important rôles. In the above cases the follicular hormone was evidently not at fault, hence its administration brought no results.

CONCLUSION

In our cases of amenorrhea accompanied by genital hypoplasia, the excretion of follicular hormone in the urine was slightly greater than

normal. Hence the administration of follicular hormone for therapeutic purposes should not, and did not, produce either a cure or an improvement in the clinical condition.

Note: Since this paper was written, similar cases were treated with very large doses of follicular hormone with the same negative result.

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1555 Grand Concourse

THE EXCRETION OF ESTRIN DURING PREGNANCY*

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IT HAS been shown by Smith[1] that from the beginning of pregnancy to the onset of labor there is an increase in the concentration of the female sex hormone in the maternal blood. The placenta was also found by Smith to contain the female sex hormone in high concentration during the end of pregnancy. It has been demonstrated, by Frank,[2] in the circulating blood of gravid women as early as the sixth to the eighth week of pregnancy.

The occurrence of the female sex hormone in the follicle liquid was first reported by Frank.[3] Its presence in the corpus luteum has been established by many workers, such as: Iscovesco,[4] Frankel and Fonda,[5] Frank and Rosenbloom,[6] etc. Estrin has also been extracted from whole ovary, fluid from ovarian cysts, amniotic fluid, urine of pregnant women, meconium, maternal feces, maternal milk,[7] human bile,[8] etc.

Since estrin has been so widely found in the excretory products of the human body and in larger quantities during pregnancy, it was decided to attempt to extract it from saliva and gastric juice of pregnant women.

Samples of saliva were taken from patients, toxic and nontoxic, during different stages of pregnancy. In order to increase the quantity of saliva, the patients were given paraffin to chew. According to Morris and Jersey[9] the act of chewing a substance such as paraffin, in addition to increasing the volume of saliva, also exerts an accelerating effect upon the process of filtration from the blood.

The following procedure was used in the extraction: To a known quantity of saliva, two volumes of 95 per cent ethyl alcohol were added. The alcohol and saliva

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were thoroughly shaken and allowed to stand twenty-four hours. The mixture was then boiled on a steam bath for thirty minutes and filtered through cotton. The cotton and precipitate were covered with 95 per cent ethyl alcohol and again boiled for thirty minutes. The filtrates were combined and evaporated to a watery sludge under vacuum. The precipitate was extracted with ether and the ether removed by exaporation. The remaining residue was suspended in oil so that 1 c.c. of the oil suspension contained the equivalent of 50 c.c. of saliva.

The method of assay used was the vaginal smear test of Allen and Doisy.[10] Three ovariectomized mature rats were used for each sample. Single subcutaneous injections were made in each case and the vaginal smears were read approximately forty hours and forty-eight hours after injection.

The samples of saliva gave the results shown in Table I.

TABLE I

TYPE OF CASE	MONTH OF PREGNANCY	VAGINAL SMEAR
Hyperemesis	$1\frac{1}{2}$	Negative
Hyperemesis (severe)	$2\frac{1}{2}$	Negative
Hyperemesis	3	Negative
Hypertension	7	Negative
Hypertension	$7\frac{1}{2}$	Negative
Normal	8	Negative
Normal	9	Negative

The chemical procedure and method of assay were next checked by using urine and saliva collected from the same patient. Ten patients were selected, all of them past the seventh month of pregnancy. Specimens were collected from four of them just before the onset of labor.

As is shown in Table II, the urine in all cases was positive for the presence of estrin while the saliva in all cases was negative.

TABLE II

NUMBER OF PATIENT	MONTH OF PREGNANCY	URINE ASSAY	SALIVA ASSAY
1	7 plus	Positive	Negative
2	$7\frac{1}{2}$	Positive	Negative
3	8	Positive	Negative
4	8 plus	Positive	Negative
5	8 plus	Positive	Negative
6	$8\frac{1}{2}$	Positive	Negative
7	Term	Positive	Negative
8	Term	Positive	Negative
9	Term	Positive	Negative
10	Term	Positive	Negative

A preparation of the female sex hormone, theelin, prepared according to the method of Doisy[11] was obtained through the courtesy of Parke, Davis and Company and an attempt was made to recover a known amount of this preparation after mixing it thoroughly with saliva. Dilu-

tions were first made of theelin, so that 1 c.c. of distilled water contained 1 rat unit, 3 rat units, 5 rat units, and 10 rat units, respectively. The dilution containing 1 rat unit to 1 c.c. of water when assayed, failed to produce a positive smear, but strongly positive smears were produced by all other dilutions.

A saliva and theelin mixture was made up, so that 1 c.c. of oil contained 3 rat units of theelin and an equivalent of 50 c.c. of saliva. When this mixture was assayed, all smears were strongly positive, showing that the female sex hormone is not destroyed by saliva.

The saliva of all cases used was alkaline to litmus paper while the urine used in every case was acid. To further check the procedure, three patients in the last month of pregnancy were given 15 grains of sodium bicarbonate three times a day for three days until their urine was strongly alkaline. Estrin was extracted from all three samples of the alkaline urine as was shown by positive smears when assayed.

A composite sample of 200 c.c. of gastric juice was collected on the fasting stomach from three patients at term. The method used in collecting the gastric juice was that of Matheson and Ammon.[12] The procedure was commenced early in the morning. A Rehfuss tube was passed and the entire gastric contents were withdrawn. One-half milligram of histamine, freshly prepared, was then given and complete aspirations were made thereafter at twenty-minute intervals. The gastric juice was subjected to the same procedure as was used in the extraction of estrin from urine and the preparation when assayed produced negative smears in all animals used.

In a recent paper Ranier[13] states that she has found the hormone of the anterior lobe of the pituitary, the folliculin hormone, and the lutein hormone in saliva of pregnant women. She feels that they are found in equivalent amounts in saliva and urine. A reference is made in her paper to an unpublished article by Zondek in which he states that the ovarian hormone and the anterior lobe hormone are present in saliva, but they are not found in gastric juice and in cerebrospinal fluid. Ranier does not use the Allen and Doisy method of assay but uses a modification of the method used by Aschheim and Zondek in the diagnosis of pregnancy. Rats and mice were injected with an extract of saliva twice daily for three or four days and then autopsied on the sixth day. In the animals used, ripe follicles were present, and there was a definite hemorrhagic condition of the genital organs.

It would seem, however, from the results obtained by using the Allen and Doisy method that estrin is not excreted from the alimentary canal above the duodenum in large enough quantities to produce the typical hornification of the vaginal mucosa.

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THE THERAPEUTIC VALUE OF AMNIOTIN IN THE MENOPAUSE

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NO SYMPTOM complex has been more resistant to treatment and none so wrapt in obscurity from an etiologic standpoint as that group of manifestations characterized as the menopause. It is only natural that clinicians should eagerly grasp at any therapeutic agent that gives promise of assistance in the alleviation of this distressing condition.

It is known at the present time that in the ovary there are several anatomical structures that are the source of different hormones. From the follicular fluid the female sex hormone, as termed by Frank, is obtained. This estrus-producing hormone has been isolated from other sources such as the placenta or amniotic fluid. From the corpus luteum have been isolated 3 hormones, one that causes the progestational hypertrophy and a second one that aids in the embedding of the ovum. A third hormone has been described in rodents which produces a softening of the symphysis. We are acquainted with the fact, that with the cessation of the ovarian function, symptoms arise which have been termed the menopause syndrome. We do not know, however, whether these symptoms are due to the absence of the ovarian hormones per se or whether the withdrawal of these substances results in a disturbance of the ductless gland system which then causes these menopausal symptoms. It seems unlikely that the corpus luteum hormones because of their very special functions can be directly associated with the menopause symptoms and it therefore leaves as the most logical etiologic factor the withdrawal of the follicular hormone as the cause of the onset of these symptoms. However, that this is not invariably so is evidenced by the fact that in some cases of primary amenorrhea, where presumably no follicular ripening takes place, there is no menopausal syndrome.

We know that the exhibition of the female sex hormone causes in animals the symptoms of estrus. On this basis it was decided to utilize amniotin in the hope that the hormone, because of its direct action or because of its effect on the other members of the ductless gland system might be of value in the treatment of the menopause.

For a number of years at the Mount Sinai Hospital there has been in existence a special clinic in the Out-Patient Department for the investigation and treatment of this symptom complex. We are here reporting a series of 43 cases treated over a period of seven months with amniotin in suppository form and by subcutaneous or deep injections. The amniotin was made available through the kindness of Dr. Anderson of the Squibb Laboratories and we wish to express to Dr. Anderson our sincerest appreciation for his interest and cooperation.

Amniotin "Squibb" is prepared from the fetal fluid of cattle by precipitation with alcohol, acetone, and ethyl ether. The resultant oil is further extracted with alcohol and benzine and the resultant filtrate contains the amniotin which can be dissolved in water. The assay is carried out according to the technic of Doisy. The rats after the injection of the material must show fully cornified vaginal smears.

We dealt exclusively with clinic patients. They reported regularly once a week and if they received injections, at least 3 times a week. The laboratory work included blood counts, urinalysis, basal metabolism, blood pressures, and x-rays, usually of joints and sella turcica, when indicated. These examinations in the clear-cut menopause case, with the exception of x-rays of the joints were essentially negative nor were they changed with amniotin treatment. Physical examinations were also done and any abnormalities found, not attributable to the menopause, ruled out these individuals as far as our studies were concerned.

Symptoms which we carefully studied included hot flushes, sweats, headaches, joint pains, insomnia, "nervousness," and libido. The patient was studied for changes in these symptoms. This was done by careful questioning each time the patient reported. Theoretically this should be an ideal arrangement, as the impersonal relationship between doctor and patient existing in the average clinic should permit unbiased observation. However, paradoxical as it may seem, in our clinic this was not the case. The only means we had of judging improvement was the patient's word. The constant contact as well as the friendly and encouraging attitude which was taken toward the patient was distinctly detrimental to acquiring objective information. Very often the patient, due to a mistaken sense of gratitude falsely said that she felt better in spite of repeated and forceful admonition to tell the truth. Mistakes were minimized whenever possible by having written records kept of the number and frequency of symptoms in order to judge the effect of treatment from a quantitative as well as qualitative angle. We have frequently seen patients brighten perceptibly as far as the general appearance and mental attitude were concerned after a period of observation during which symptoms may have only been moderately improved. This we are inclined to attribute to contact with the doctor. As can readily be seen, the patients will tell not only symptoms but their other troubles as well, and this opportunity to relieve their minds may have

played an important part in influencing improvement. This psychic element, if we may use the term, strikes us as being exceedingly important. The fact that trouble at home, or periods of stress have resulted in an exacerbation of symptoms, where previously there has been apparently steady improvement only serves to emphasize this point.

In a previous report of a series of 25 cases treated with amniotin Sevringhaus and Allen reported satisfactory results in 14 cases, especially in those with vasomotor disturbances.

Our series comprises 43 cases. In 10 cases there was no improvement, in 22 cases there was varying improvement, and in 11 cases there was considerable improvement. In the last group of 11 cases the improvement was related to the appearance of vaginal bleeding after treatment. It is of interest to analyze the various groups so that a more rational understanding of the role played by the amniotin may be arrived at.

In the group of 10 cases showing no improvement there were 5 cases due to radiotherapeutic castration. In these, suppositories were used either alone or in combination with injections. In one instance, because of the very high blood pressure, 220/120, the patient was finally referred to the medical department. Two of these received 240 rat units as an injection dose, the other 300 rat units. Three operative cases received suppositories with no obvious improvement. In one instance the patient seemed better for about six months and then grew worse. The last two cases were natural menopause. In one the relief from amniotin was slight and transient, the symptoms aggravating under treatment which was stopped after six weeks. The second patient complained of pruritus vulvae which had resisted all treatment including x-ray. There was some atrophy of the skin but no real kraurosis. For a period of two and one-half months she received amniotin suppositories in doses as high as 160 rat units a day with no relief.

In the group of 11 cases that showed considerable improvement 10 were associated with bleeding, 1 was not. This latter case was a patient with kraurosis vulvae who, after medical treatment and x-ray, finally had a vulvectomy. The itching reoccurred after operation. She received amniotin injections over a period of two months, the dosage being as high as 200 rat units per injection 3 times a week. The improvement was steady and striking. The other 10 patients of this group that showed improvement are difficult to analyze. All these patients had temporary periods of improvement, noted either just before or during the time of vaginal bleeding. Just what role the amniotin medication played in the production of the bleeding cannot be definitely evaluated as we were unable by interrupting the treatment and resuming it to regularly cause the appearance of vaginal bleeding. This in great part is due to the fact that the patients were irregular in their attendance. However, it does seem more than coincidence that 10 of 43 patients in our series should bleed, and it is fair to conjecture that amniotin may

have precipitated vaginal bleeding by simulating menstruation in the menopausal state with at least temporary relief of symptoms. This is borne out by the work of Allen and Baker who produced menstruation in castrated monkeys using amniotin suppositories in doses approximating ours. A brief analysis of 3 of these cases may be permissible.

The first patient had a natural menopause and had a persistence of her symptoms under amniotin treatment. After being amenorrheic for six months, she had a period of bleeding with relief of symptoms. Then in spite of further treatment over a period of five months there was no recurrence of the bleeding and no alleviation of her symptoms.

The second case was an x-ray menopause. She had injections up to 120 units twice a week, improved for two months and then bled with complete relief of symptoms. Treatment was then stopped and patient remained well except for occasional flushes.

The third case was an x-ray castration. The patient had severe symptoms for one year. She received suppositories and was immediately improved. After one month of treatment she again showed improvement and bled.

It can be seen that it is difficult to determine the role played in alleviation of symptoms by the use of amniotin. The bleeding and relief of symptoms might have occurred without treatment. On the other hand the question arises whether the amniotin initiated the necessary changes that produced bleeding and so caused an improvement or whether the hormone itself was directly responsible for the improvement. It is evident that the benefit in most instances was transient.

In a group of 22 cases the improvement shown was slight in most instances and not permanent. In some, it was possible that the psychic effect of the treatment may have resulted in a temporary relief of symptoms. In some instances blank suppositories were used, but all these patients stated that they were not helped by these suppositories even though they were not aware of the fact that there was no medicament in the suppositories. However, in several instances the improvement was striking, rapid, and of long duration. One patient (22495) an x-ray castration had treatment for six weeks with amniotin with complete relief of symptoms. These recurred to be relieved again when amniotin was repeated. Another patient (22219) an operative castration had severe symptoms. She improved rapidly after one week of treatment. When the suppositories were stopped, the patient stated there was a distinct change. These cases require no detailed explanation but it can be stated that in this group of 22 cases amniotin in suppositories or injections seems to have been of some benefit. In some the relief was only temporary, ceasing when amniotin was discontinued and not improved when they again received the medication. Others showed improvement in some symptoms, particularly the flushes and sweats, while other manifestations such as headaches, joint pains and nervousness continued or increased. In still another group the symptoms improved under amniotin, to reappear when the treatment stopped and again were relieved on the resumption of treatment.

To summarize the effect of amniotin in the treatment of the menopausal syndrome, we may say that in one group of cases it seems to have influenced a return of the menstrual period with a temporary relief of symptoms; in other cases it caused a distinct alleviation of symptoms while the substance was exhibited, but the relief was not of a permanent nature. What influence the psychic effect of the treatment played is hard to evaluate. However, it is evident that the substitution of a single hormone, that is not being produced by the individual, is not sufficient to prevent entirely the symptoms of the menopause, and it is certain that other factors are included in the problem of the menopause and its associated symptoms. However, in comparison with the other therapeutic agents at this clinic, which has been in operation for seven years, amniotin is distinctly superior.

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THERAPEUTIC VALUE OF THEELIN IN THE MENOPAUSE

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THE premise that menopause symptoms are associated with a cessation of ovarian function is both reasonable and logical. As a corollary it may be stated that the loss of the dominant ovarian secretion, the female sex hormone, would appear to be a most important factor, although the increase in pituitary hormone must be taken into account. On this basis, attempts to replace this loss of female sex hormone by a substitution therapy are surely indicated. Results obtained with amniotin, biologically potent sex hormone preparation have been previously studied by us. We were led to conclude that in one group of cases it seemed to have influenced a return of the menstrual period with a temporary relief of symptoms, in other cases it caused a distinct alleviation of symptoms while the substance was exhibited, but the relief was not of a permanent nature. What influence the psychic effect of the treatment played is hard to evaluate. However, it is evident that the exhibition of a single hormone, that is not being produced by the individual, is not entirely sufficient to prevent the symptoms of the menopause, and it is certain that other factors are included in the problem of the menopause and its associated symptoms. However, in comparison with the other therapeutic agents used at our clinic, which has been in operation for seven years, amniotin proved distinctly superior.

Theelin, another excellent follicular hormone preparation, was used in the studies on the present series of cases. It represents the purest product obtainable, and assays as labelled, 50 rat units per c.c.

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*Manufactured and supplied by Parke, Davis & Co., Detroit, Michigan.

The preparation was administered by intramuscular injection in increasing doses beginning with 50 rat units, three times weekly. The patients were always carefully interviewed regarding the effects of the injections in regard to exacerbation or improvement of symptoms. Before treatment complete physical examinations, blood pressure readings, complete blood counts, basal metabolism, x-rays of sella turcica and joints when indicated, and weight were recorded. The symptoms which were stressed and which were usually present were hot flushes, sweats, headaches, joint pains, insomnia, palpitation, libido, paresthesias, and psychic disturbances. The frequency of examination and administration of the material gave ample opportunity for observation of the patients. The majority were observed and treated from four to eighteen weeks, four only for three weeks and one for one week. Six cases were not strictly of the menopause type, but were included because their complaints were closely associated with menopause symptoms.

RESULTS

TABLE I. ALL CASES TREATED

CASES TREATED	TOTAL	MARKEDLY IMPROVED	SLIGHTLY IMPROVED	NO IMPROVE-MENT	IMPROVED WITH BLEEDING
Menopause	25	4	9	9	3
Kraurosis	2	2			
Primary Amenorrhea	2			2	
Secondary Amenorrhea	2			1	1

TABLE II. MENOPAUSE CASES

TYPE	TOTAL	MARKEDLY IMPROVED	SLIGHTLY IF AT ALL IMPROVED	UNIMPROVED	IMPROVED WITH BLEEDING
Natural	14	4	4	3	3
Artificial	11		4	5	

COMMENT

Scrutiny of the above statistical study would appear to justify the conclusion of the existence of an efficacious hormonal preparation useful in the menopause. Certainly an improvement in 19 of 31 cases treated should be evidence of its value. Studies by other observers on this and similar preparations have almost invariably resulted in favorable reports. Where the patient's word alone is the sole means of determining improvement, and where the symptoms were almost never severe enough to incapacitate the individual, an exceedingly fine sense

of judgment must be brought into play. The correct evaluation of symptoms is so complicated that definite conclusions are difficult to draw. So many other factors enter into the patient's physical status in the menopause that it is only by unceasing and untiring effort that results worthy of attention may be arrived at.

It is insufficient to ask the patient, "How do you feel?" and to accept the reply, "Better," as evidence of improvement. The number of flushes, sweats, headaches, etc., may remain the same. The reason that the patient felt better was often found to be some happy event, good news, or improvement in her environment; in other words, improvement in her mental state which temporarily at least focussed her attention on something other than her symptoms. This mental factor is to be regarded as of prime importance. One of the greatest difficulties arose from the fact that the patients were seen so frequently and over such a long period of time. Most of them were grateful for the treatment and the interest shown, even to the point of recording improvement in order, as they thought, to please the physician. The facts were ultimately arrived at with considerable difficulty.

The nine cases reported as slightly if at all improved are of little value. For the sake of accuracy they have to be designated as improved. Actually the improvement was so slight and referred to minor symptoms, or was so transient as to really be negligible. The symptom upon which most stress was placed was the heat flash. This was the only one that could be exclusively associated with the menopause. The headaches, joint pains, palpitation, paresthesias, loss of libido, etc., brought so many other factors both physical and mental into question that they were not ranked equal in importance with the flushes. Often they had been present for years before the onset of the menopause, and here it was invariably noted that the menopause was an aggravating factor.

As far as improvement in the individual symptom is concerned, it was found that the joint pains were almost never improved, headaches rarely, sweats only with improvements in flushes; palpitation, paresthesias, and insomnia were improved more often. A return or an increase in libido was occasionally noted. As has been stated, the change in flushes was regarded as the important criterion.

It is interesting to note that the natural menopause appears more amenable to treatment than the artificial. Of the 14 cases treated (Table II) 11 were improved, 7 markedly so. Here also it was observed that in 3 of these cases the menstrual periods were reestablished with complete alleviation of symptoms. The follicular hormone probably was a factor in the production of this result, although the possibility that it may have occurred purely by coincidence must be entertained. The artificial menopause cases, either operative or x-ray castrates, were little affected. These patients showed the most severe

symptoms, really not to be compared with the relatively mild symptoms of the natural menopause.

The two kraurosis cases on whom vulvectomy had been performed showed marked improvement in the symptom complained of, "itching." This was also found to be true under amniotin treatment. Undoubtedly, supplying the follicular hormone is the important factor. The four amenorrheic cases require little comment. In three, treatment was entirely unsuccessful and the fourth bled convincingly on several different occasions with administration and withholding of the hormone.

The dosage used in the studies appeared to be ample. As much as 400 rat units per injection was given. Its constant use over a long period of time would be sufficient.

BRIEF ABSTRACT OF HISTORIES OF CASES SHOWING ANY IMPROVEMENT

CASE 1.—D. M., aged thirty-three, married. This patient had a vulvectomy in 1926, for kraurosis. Following this operation pruritis persisted. She was given twelve injections of theelin in increasing doses, with marked improvement.

CASE 2.—R. C. This patient is fifty-four years of age, married, had vulvectomy for kraurosis. Symptoms continued. She was given amniotin pessaries in April, 1930 with considerable relief. In May, 1930, her symptoms were still present for which theelin was given from May 7 to June 4 in increasing doses up to 250 rat units per injection with striking improvement.

CASE 3.—R. G., aged forty-two, married, artificial menopause (by radiotherapy) in December, 1930. Complained of frequent flushes, sweating, headaches present for a long time, joint pains in right elbow, palpitation, psychic disturbances, and insomnia. Physical examination essentially negative. Basal metabolism plus 17 per cent. Uranalysis negative. Weight 140. This patient received 9 injections of theelin in increasing doses to 250 rat units per injection from May 15 to June 8, 1931. There was slight improvement in the symptoms but these originally were very mild.

CASE 4.—A. S., aged fifty, married, natural menopause, August, 1928. Symptoms were as follows: Flushes, 20 to 30 per day, accompanied by sweats, headaches present for fifteen years, worse since menopause. Joint pains also present for fifteen to twenty years. Insomnia slight. Physical examination negative. Blood pressure 135/105. Weight 150. Uranalysis essentially negative. Basal metabolism normal. Blood count showed hemoglobin of 65 per cent and lymphocytes, 52 per cent, otherwise normal. She was treated with sedatives, at first, then thyroid with improvement. She received 14 injections, from February 19 until March 12, 1931 in increasing doses up to 150 rat units per injection. There was slight improvement.

CASE 5.—A. C., aged thirty-seven, married, artificial menopause (operated upon five years ago, 1926). Complained of flushes 20 per day, profuse sweats, headaches, joint pains in hands, palpitation, insomnia. Libido decreased. Physical examination negative. Blood pressure 140/95. Urine negative. Basal metabolism plus 6 per cent. Blood count normal, except for 50 per cent of lymphocytes. This patient received 8 injections of theelin in increasing doses up to 200 rat units per injection between April 27 and May 18, 1931. There was slight improvement in symptoms.

CASE 6.—E. B., aged forty-three, married, natural menopause January, 1930. Complained of flushes one to two per day, sweats not marked, headaches, joint pains, occasional insomnia. Physical examination, except for a blotchy skin with acne was essentially negative. Blood pressure 136/80. Blood count normal. Basal

metabolism minus 3 per cent. Uranalysis negative. She received 100 rat units per injection. She stated that she felt better but original symptoms were very mild.

CASE 7.—E. G., aged thirty-eight, married, natural menopause December 15, 1931. This patient complained of 3 flushes per day, occasional headaches, joint pain in left shoulder, present before cessation of menses. Slight palpitation, psychic disturbances, insomnia. Libido present. Physical examination negative. Basal metabolism minus 4 per cent. Blood count normal. Blood pressure normal. She received 14 injections from March 3 until May 25, 1931. There was slight improvement in symptoms, which were originally mild.

CASE 8.—H. L., aged thirty-one, married, artificial menopause November, 1925 (intrauterine and vaginal radium for endometriosis). Flushes every five minutes. Sweats without flushes, headache (frontal), continuous backaches, palpitation, psychic disturbances, insomnia. Libido unchanged. Physical examination negative. Blood pressure 112/70. Weight 129. Basal metabolism normal. Blood count normal. This patient has been under treatment since 1928. She received placebos and in 1929, she was admitted to the neurologic service of the hospital where she was studied and finally discharged, with no diagnosis being made although abnormal neurologic signs were found. She reported back to the menopause clinic and was placed on theelin which she received from March 9 to June 22, 1931. A total of 23 injections up to 300 rat units per injection were given. At the end of treatment, flushes had decreased to about 3 per day. However, headaches, joint pains, insomnia, and palpitation were still unrelieved. The patient was moderately improved.

CASE 9.—A. S., aged forty-seven, married, weight 147, natural menopause, January 30, 1931. Symptoms appeared September, 1930, flushes every half hour, sweats, headaches, joint pain in right shoulder, palpitation, marked insomnia, libido absent. Physical examination essentially negative. Blood pressure 142/78. Basal metabolism minus 21 per cent. Uranalysis negative. Theelin was begun April 18, 1931 and was continued until April 27, 1931. She received 6 injections with slight improvement. In view of the basal metabolism, minus 21 per cent, she was placed on $\frac{1}{4}$ gr. of thyroid T. I. D.

CASE 10.—R. L., aged forty-seven, married, natural menopause April, 1930. Symptoms began at about that time. They included flushes, profuse sweats, headaches, pain in left knee, psychic disturbances and insomnia. Blood count and basal metabolism not done. Physical examination negative. Patient still has occasional periods of bleeding. She received theelin from April 27, 1931 to June 8, 1931, receiving nine injections up to 250 rat units per injection. She improved so that all symptoms disappeared except the joint pain. She then bled from May 23 to May 26. When seen subsequently, she was having only two mild flushes per day. In this case the improvement associated with the bleeding was so marked that further treatment was stopped.

CASE 11.—R. R., aged forty-three, married, natural menopause February 15, 1931. Symptoms immediately after these included ''frequent'' flushes, severe headaches, joint pains in elbow and palpitation and insomnia. Physical examination essentially negative. Blood pressure 165/100. Weight 191. Basal metabolism minus 25 per cent. Complete blood count normal except for eosinophiles of 5 per cent. She received theelin from June 8 until August 20, three times a week, 9 injections all together up to 300 rat units per injection. Symptoms were mild. Under treatment they completely disappeared according to her statement at the last examination. This patient was very cooperative and very grateful for the treatment received. This probably influenced improvement considerably.

CASE 12.—A. K., aged forty-two, married, natural menopause five years ago. Complained of flushes every one-half hour, sweats, backache, palpitation, insomnia,

libido absent. Basal metabolism plus 16 per cent. Complete blood count normal. Blood pressure 165/115. Physical examination essentially negative. Received eight injections between August 31 to September 26, 1931, dose gradually being increased to 300 rat units per injection. This patient improved considerably. At the last examination, no other symptoms except palpitation were present.

CASE 13.—A. M., aged forty, married, natural menopause, period in December, 1930 then March 4, 1931. She complained of flushes, sweats, pains in the elbow and feet and palpitation. Some insomnia. Physical examination is negative. Basal metabolism minus 3 per cent. Uranalysis negative. Blood count normal. This patient received 7 injections of theelin up to 200 rat units per injection from April 13, to May 11, 1931, during which time she had two episodes of bleeding with complete alleviation of symptoms. As she was menstruating, treatment was stopped. Theelin was probably a factor in causing the bleeding. Her symptoms aside from the time she was bleeding, were only slightly improved.

CASE 14.—B. B., aged forty-four, married, natural menopause June 1930. Symptoms appeared August, 1930. Complained of flushes five times daily. Headaches, joint pains in arms, leg and back, palpitation, psychic disturbances. Libido always absent. Physical examination negative. Blood pressure 156/90. Basal metabolism minus 4 per cent. Blood count except for 43 per cent of lymphocytes was normal. Urine negative. She received 15 injections of theelin up to 150 rat units per injection. She showed some improvement. Flushes were reduced to one or two per day and other symptoms were also improved. She also reported increased libido. She then had a period in April and another period in May. Treatment was discontinued as symptoms disappeared with the bleeding.

CASE 15.—M. D., aged twenty-five, single. A case of secondary amenorrhea. This patient menstruated every seven to twelve months. She showed kyphosis, hirsutes, girdle obesity. Basal metabolism varied from plus 2 per cent to minus 15 per cent. Urine negative except for trace of albumin and moderate white blood cells on several occasions. Thyroid was not well tolerated and produced no effect. She also received antuitrin injections which was followed by staining after 10 injections on October 18, 1930. No bleeding occurred until she received theelin from January 22 to February 2, 1931, on which date she began to bleed and bled for one day. This occurred after 5 injections. Theelin was then discontinued in order to see if patient would have a period the following month. As she did not menstruate, treatment started again on March 9, 1931. She received 12 injections up to March 29 when treatment was stopped in order to watch for effect. She again spotted on April 6 and 7. She then received several large doses of theelin up to 200 rat units and then bled again, June 1, 1931. Her various other complaints resulted in her being admitted to the hospital where she was laparotomized by the surgical service for a pelvic tumor which was not found. It is very likely that the episodes of bleeding in this case, were produced by the injections of theelin. They were proved menstrual periods as uterine mucosa was found in the hemorrhagic discharge.

CASE 16.—A. M., aged thirty-eight, married, artificial menopause (radiotherapy July, 1930). Symptoms soon after. She complained of three or four flushes per day, headaches, sweats, joint pains in the elbows and insomnia. Physical examination essentially negative, except for tenderness over left elbow joint and a somewhat hypertrophied heart. Blood pressure 112/76. Basal metabolism minus 3 per cent. Urine examination negative. Blood count normal. She received 6 injections from March 26 to April 6, 1931 in increasing doses to 150 rat units per injection. At the end of treatment, the patient was very moderately improved, but was still having

occasional flushes, headaches, and joint pains. In this case the patient's psychic condition was also considerably improved.

CASE 17.—D. L., aged forty-four, married, natural menopause, May, 1929. Symptoms immediately afterward including moderate flushes, some sweats, headaches, stiffness in the joints, moderate palpitation, insomnia. Libido present. Physical examination negative. Blood pressure 160/90. Weight 149. Basal metabolism minus 2 and 1 per cent. This patient from the very beginning showed a marked globus hystericus with associated nervous symptoms which were entirely uninfluenced by treatment and were based on difficulties at home with her grown children. She received 15 injections between January 12 and February 16, 1931, in increasing doses up to 125 rat units per injection. Improvement was marked, the only symptoms which persisted were joint pains and insomnia. Hysterical condition was not affected, but patient responded very well to the interest shown in her case which probably influenced the improvement.

SUMMARY AND CONCLUSIONS

1. Thirty-one cases, of which 25 were menopausal, were studied in order to determine the effect of theelin, a biologically potent female sex hormone preparation.

2. The evaluation of improvement or nonimprovement in menopause symptoms as a basis for judgment of the efficacy of the preparation was found to be exceedingly difficult.

3. Seven menopause cases of the 25 patients were definitely improved, 3 with the reestablishment of menstruation. The others were either unimproved or so slightly improved as to be negligible.

4. Two patients with kraurosis on whom vulvectomy had previously been performed showed marked improvement of the itching.

5. Three of 4 amenorrheic patients were unaffected as far as return of menstruation was concerned. The fourth bled convincingly, probably attributable to the material used.

6. In several cases of natural menopause, bleeding, possibly menstruation, followed the injection of theelin.

7. The natural menopause seems to be more amenable to treatment than the artificial climax.

8. Substitution of the female sex hormone alone does not in all cases relieve the menopause syndrome.

9. Other factors such as reduction of the quantity of anterior pituitary hormone may improve the results.

100 EAST SEVENTY-FOURTH STREET

A FURTHER STUDY OF THE ANTERIOR PITUITARY SEX HORMONES

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EXPERIMENTS with anterior pituitary hormones as detected by the original technic of Aschheim and Zondek and its modifications have been in progress in this department since January, 1929. These experiments together with a complete résumé of the literature to date have been discussed recently by T. K. Brown.[1] He reported our use of the female rabbit as the test animal in preference to immature white mice and the use of blood serum as the test substance in preference to urine.

Throughout our work the guiding principle has been that of an experimental study rather than purely a clinical test. Mice, rabbits, and guinea pigs have been used as test animals. Urine, blood serum, blood plasma, extracts of blood serum, plasma and urine, ovarian cyst fluid and extracts of the same and cerebrospinal fluid have been used as test material. We have employed the subcutaneous, intravenous, and peroral routes of administration. Test materials have been taken from cases of suspected and known pregnancy from five days after a missed period to term, ovarian cysts, ovarian cysts complicating pregnancy, extrauterine pregnancy, hydatidiform moles, incomplete, complete, threatened and missed abortions, and amenorrheas due to various causes.

As a result of these studies the routine procedure evolved in this laboratory consists of one intravenous injection of 2 to 3.5 c.c. of blood serum into a virgin female rabbit weighing between 1500 and 1600 gm. Our work with the rabbit was initiated following a report of Scott and Reinhart[2] in June, 1930, and entirely confirms the earlier conclusions of Friedman[3] who, in 1929, suggested the substitution of the rabbit as the test animal of choice in this work. Schneider[4] and Reinhart and Scott[5] in recent publications also report satisfactory results with the use of the rabbit as the test animal. All of these investigators use urine as the test material. Zondek,[6] in a complete review of his work, mentions the use of blood serum injected subcutaneously into mice. We feel that the use of blood serum removes several of the variable factors in the test and simplifies the procedure. We have, thus, a test substance which is sterile, can be given in small doses and removes any possible doubt as to the source of the material. If the degree of reaction can be taken as an index of the concentration of hormone present there is, apparently, a higher concentration in the blood than in the urine. Reinhart and Scott[5] in their most recent article state that "luteinization of the rabbit ovary begins between the forty-eighth and ninety-sixth hours after injection."

This is true for urine injected intravenously. However with blood serum intravenously, in practically every test well developed luteinization occurs before forty-eight hours.

In earlier experiments small rabbits were used. One series of does weighing between 600 and 900 gm. tested with known pregnancy serum gave entirely irregular and wholly unreliable results. In the entire series of tests performed for clinical diagnosis to date, there have been only two false reactions. Both these tests were performed with blood serum from the same pregnant patient. The does weighed 1140 gm. and 1200 gm. respectively and the tests were completely negative. These are considered false reactions because does of 1200 gm. usually are reliable test animals. We agree with Schneider and Reinhart and Scott with regard to the weight of the rabbits. In our present work rabbits of 1500 to 1600 gm. are used and are entirely satisfactory.

Zondek,[6] 1930, described methods for concentration and detoxification of urine for the "pregnancy test." The urine is precipitated with 95 per cent alcohol, centrifuged and the sediment is washed with ether. The remaining sediment is dissolved in a fraction of the original volume with water. The anterior pituitary hormones are found in this aqueous solution. Zondek also discusses the physical properties of these active substances. They are easily dialyzable, do not pass through a Berkefeld filter, are destroyed at 60° C. and are adsorbed onto Kieselguhr and charcoal. These properties aid in the differentiation of the pituitary sex hormones from the growth hormone and the ovarian sex hormone.

In performing the test with blood serum as described above, it was noted that occasionally a rabbit died immediately after or within an hour after injection. This death was thought to be due, solely, to an overload of protein material thrown into the vascular system at one time. This "protein shock" was usually noted when smaller rabbits were used and when more than 3.5 c.c. of serum was injected. That this undesired reaction was not due to an increase in the volume of the circulation was known because 10 c.c. or more of urine can be injected without any danger. Referring then to the Zondek technic for concentration of urine, blood serum was treated in a similar manner. One volume of blood serum or plasma, usually 10 c.c., is precipitated with ten volumes of 95 per cent alcohol, shaken vigorously, allowed to stand for half an hour and centrifuged. The alcohol is drawn off and the sediment shaken with five times the original volume of ether and centrifuged again. After pouring off the ether, water or normal salt solution is added to the ether-washed sediment in the same volume as the original volume of serum. This final mixture must be centrifuged rapidly and for at least forty minutes to throw down a gelatinous residue, protein in nature. The supernatant fluid is a greyish, murky, aqueous solution containing the active principles desired. That this solution is not yet protein-free can be demonstrated very easily by reprecipitation with alcohol. A

large amount of protein is removed in this procedure and extracts prepared in this manner can be administered in much larger doses than a corresponding serum. As much as 8 to 10 c.c. of such extracts have been injected intravenously at one time and the degree of reaction in the ovary has been, in most cases, proportional to the volume, when compared with the reaction resulting from 3.5 c.c. of serum.

RESULTS

In this series there are 65 tests to be reported:

Clinical Diagnosis		Test Substances	
Pregnancy	20 Cases	Blood serum	38
Abortions	10	Extracts	12
Ovarian cysts	10	Urine	6
Ovarian cysts and		Cerebrospinal fluid	4
Pregnancy	5	Cyst fluid	2
Tubal abortion	4	Miscellaneous	3
Amenorrhea	5		—
Sarcoma of bone	4		65
Miscellaneous	7		
	—		
	65		

Analyzing the results in this series, from the point of view of diagnoses there are twenty tests for pregnancy. Four of these tests were performed with cerebrospinal fluid and are part of a series reported previously, all of which revealed a Type I reaction, i. e., follicle formation without associated hemorrhage or corpus luteum formation. Six tests in this group were carried out with extracts of blood serum, plasma or urine as the test material. In five of these six, the doe was used and from 4 c.c. to 8 c.c. of the extract was injected into a marginal ear vein at one time. In all cases Type II and Type III reactions resulted within forty-two hours. In one test with an extract of series of immature female white mice was used and injections of 1 c.c. were made on each of two successive days. Autopsy at ninety-six hours revealed a Type III reaction. Ten animals were injected with 3.0 to 3.5 c.c. of blood serum intravenously and with two exceptions Type II and III reactions were noted. These two negative and false tests were obtained with the serum of a pregnant woman and have been discussed above. The explanation of the false reaction lies undoubtedly in the small size of the animals used. Since we have used does of 1500 to 1600 gm. weight no such error has been observed.

There are ten cases of abortion. The "pregnancy" reaction becomes negative about five to seven days after complete abortion. In the absence of sufficient clinical findings or as an aid thereto a positive test becomes useful as an index to the presence of attached decidual tissue. The diagnosis of missed abortion can be made in those cases where a positive test is followed, after an interval of time, by a negative test. Here, too, clini-

cal findings and laboratory information can be correlated. In this group of tests hemorrhagic follicles and corpus luteum formation were obtained when tissue was still present in the uterus, as proved at curettement. Blood serum and extracts were equally reliable.

Ten cases of ovarian cyst revealed, uniformly, a Type I reaction. In this group blood serum and rabbits were used. Ovarian cysts complicating pregnancy returned the same reaction as pregnancy. The cyst fluid and an extract of the same from one of these cysts removed at operation when the patient was sixteen weeks pregnant revealed a strongly positive Type II and III reaction.

Three cases of old tubal abortion resulted in negative or Type I reactions. A fourth such case, of only a few hours' duration, was tested by injecting the free bloody fluid found at operation. A marked Type II and III reaction was observed.

Five tests performed for an amenorrhea of only a few days returned Type I reactions and all were substantiated by a subsequent menstrual flow. One menopause amenorrhea resulted in a mild Type I reaction. Cancer of the cervix revealed marked Type I reaction with both serum and extract. Two cases of hydatidiform mole were reported previously and gave the same reaction as pregnancy.

Concerning the peroral route of administration, Zondek[6] has been able to obtain Type I and Type III reactions by feeding Prolan to infantile rats, but similar results could not be obtained with mice. Only Type I reactions were observed in mice and then only when large doses of Prolan were fed. Janssen and Loeser[7] reported Type III reactions without hemorrhagic follicles when 20 to 35 gm. female rats were fed an acetone dried powdered anterior pituitary gland. Our own experience with peroral administration is as yet insufficient to report.

SUMMARY AND CONCLUSIONS

Reviewing our entire experiences with over 200 experiments and tests, we emphasize the importance and reliability of this test. No conclusions can be drawn as to the nature of the hormone or hormones except that they are water soluble and are probably adsorbed onto protein.

The doe, weighing about 1500 to 1600 gm. has proved to be the best test animal, blood serum the best test material and intravenous injection the best route of administration.*

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*Since this report was written, an additional 150 tests have been done. In the total of 350 tests there were only two false reactions, noted above.

THE ASCHHEIM-ZONDEK REACTION IN RABBITS

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THE only real drawback to the pregnancy test of Aschheim and Zondek, from the practical viewpoint, is the length of time (one hundred hours) required for its completion.

Much of the recent work on this subject has dealt with the problem of reducing this interval. Zondek has obtained results in fifty hours by a rather elaborate method of concentrating the substance responsible for the reaction. He can place reliability, however, only on positive results. Eberson, using a similar method of concentration and employing immature rats as the test animals has claimed results in thirty-six to forty-eight hours.

Friedman and Lapham, in a recent article, report excellent results in forty-eight hours, using rabbits as the test animals. Their technic is by far the most simple of the rapid methods and requires no elaborate method of concentration. Schneider, employing the technic originally outlined by Friedman, obtained results in twenty-four hours and even speaks of the possibility of twelve hours. Reinhart and Scott have likewise used this method and report favorably.

Our study was undertaken to determine the reliability of the technic originated by Friedman and also to ascertain the shortest interval that would give dependable results. The material presented is based on 163 tests made on 101 different patients. The series includes positive and negative controls, clinical tests and various experiments relating to concentration of urine and reliability of test animals.

TECHNIC

At the beginning of the study we employed the very simple technic used by Schneider. This consisted of the injection of 5 to 7 c.c. of an early morning urine specimen of the patient to be tested into the ear vein of an immature female rabbit. The age of the animal was specified as twelve to fourteen weeks. Our results with this technic were not absolutely satisfactory. Several errors were encountered which seemed, in the main, to be due to two factors.

The first of these appeared to be the faulty specification of the test animals. We found that some rabbits, though definitely of the age limit twelve to fourteen weeks were too poorly developed to be satisfactory. The second factor seemed to be explained by the disregard of the concentration of the urine as indicated by the specific gravity.

To compensate for the latter, we increased the amount of urine injected when the specific gravity was low. The technic was changed so that 5 or 7 c.c. were injected only when the specific gravity was above 1.025; 15 c.c. were used when the specific gravity was between 1.015 and 1.025; and 20 c.c. when the specific gravity was below 1.015. These increased amounts were injected in three or four doses over a period of four or six hours.

In the matter of test animals, we have changed the minimum requirement to fourteen weeks of age and 1500 gm. in weight. As Friedman has shown, however, any female mature rabbit may be used providing she is not pregnant. At present we are using immature animals of the above specifications, post-partum rabbits, or any female animal that has been isolated long enough to rule out pregnancy. If circumstances have not allowed an isolation of at least three weeks, we have laparotomized the animals to rule out pregnancy.

Table I presents the data on the basis of which the changes in technic were made. The size of the ovaries was known in 99 test animals of the age limit twelve to fourteen weeks. We have arbitrarily taken the size of the ovaries as an index of development and divided the animals into two classes, using 1 cm. as the dividing line. The marked difference in the percentage of correct results is shown in Table I.

TABLE I.   TWELVE-TO-FOURTEEN-WEEK-OLD RABBITS

OVARIES 1 CM. OR LESS						OVARIES OVER 1 CM.					
5 C.C. 24 HR.			5-20 C.C. 24 HR.			5 C.C. 24 HR.			5-20 C.C. 24 HR.		
NO.	ERROR	CORRECT	NO.	ERROR	CORRECT	NO.	ERROR	CORRECT	NO.	ERROR	CORRECT
11	4	64%	21	8	62%	29	4	87%	38	3	92%

Low Specific Gravity

Case 39	2 mo. Pregnant	2-22-31	5 c.c.	Sp. Gr. 1.005	Test Neg.
		2-28-31	17 c.c.	Sp. Gr. 1.001	Test Pos.
Case 48	4 mo. Pregnant	2-24-31	7 c.c.	Sp. Gr. 1.005	Test Neg.
		2-28-31	16 c.c.	Sp. Gr. 1.009	Test Pos.
Case 29	2 mo. Pregnant	2-15-31	5 c.c.	Sp. Gr. ?	Test Pos.
	Threatened abortion	2-26-31	5 c.c.	Sp. Gr. 1.004	Test Neg.
		2-28-31	18 c.c.	Sp. Gr. 1.004	Test Pos.

The second part of Table I shows the effect of low specific gravity in three of the cases. All test animals in this group had ovaries over 1 cm. In the first two cases (Cases 39 and 48) different specimens of urine were used. In the last patient, however, on whom a positive result had been obtained two weeks before a threatened abortion developed, the same specimen was used for the two tests. Our work on this particular phase of the subject has not been completed, but at present it would seem that lack of concentration of the active substance in low specific gravity urines may be a factor in some of the errors.

INTERPRETATION OF FINDINGS

In clinical application, we are at present allowing the test to run forty-eight hours unless there is a request for a more rapid diagnosis. The animals are either autopsied or laparotomized. In interpreting the test, ovarian follicles, regardless of size are disregarded. Likewise, in the mature animals, old corpora lutea have no significance. The result is considered positive only if there is unquestionable evidence of fresh hemorrhage into one or more follicles.
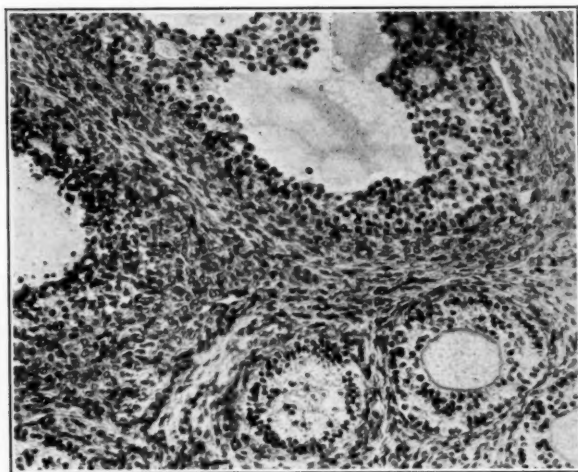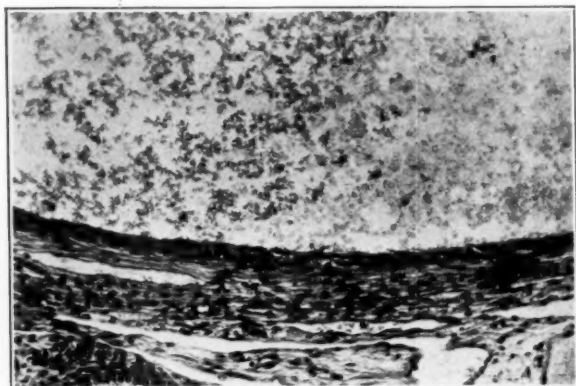
Fig. 1.—Section of normal ovary of rabbit (×185).

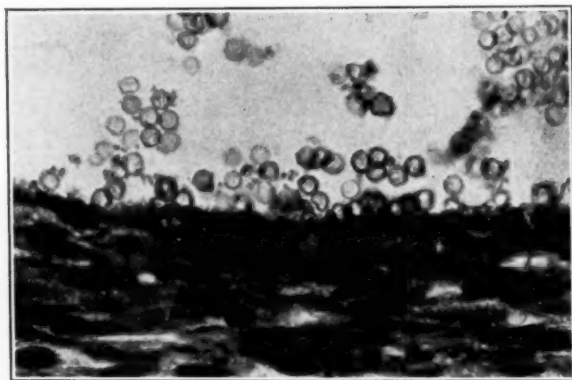Fig. 2.—Section of rabbit ovary, showing appearance of hemorrhagic follicle of a positive reaction (×185).

Fig. 3.—Same as Fig. 2 (×750).

Congestion of the uterus and ovaries is present relatively frequently in positive cases but cannot be relied upon as significant, since it may also be found in negative tests. When the animals are operated upon rather than autopsied, congestion of the ovaries may give some difficulty in interpretation of the test unless it is markedly positive. We have overcome this to a certain degree by using sodium amytal in place of ether-chloroform inhalation anesthesia.

On rare occasions we have encountered small blackish areas in the ovaries, even in immature rabbits. These are apparently old hemorrhages and are not to be confused with the recent hemorrhage of a positive result. While this finding is rare, it is of importance, because such tiny black spots must be disregarded in the interpretation of the test.

The macroscopic findings were checked in the first 100 cases by microscopic sections. The appearance of a normal follicle is shown in Fig. 1, while hemorrhage into the follicle (positive test) is illustrated in Figs. 2 and 3. We do not section the ovaries now unless we are unable to make a definite diagnosis macroscopically.

RESULTS

We have tabulated the results of 123 clinically proved cases according to the technic used. The figures are based on the normal pregnancy and

TABLE II. CONTROL, TWENTY-FOUR HOURS (48)

PREGNANT (NORMAL)	POSITIVE					NEGATIVE			
	5 C.C.		5-20 C.C.			5 C.C.		5-20 C.C.	
	NO.	ERROR	NO.	ERROR		NO.	ERROR	NO.	ERROR
2 Months	3	0	3	0	Male	1	0	1	0
3 Months	1	0	0	0	Female Norm.	2	0	0	0
4 Months	3	2	8	2	Female Menst.	0	0	1	0
5 Months	2	1	3	0	Metrorrhagia	0	0	2	0
6 Months	2	1	0	0	Menorrhagia	0	0	1	0
7 Months	1	0	2	1	Subinvolution	0	0	2	0
8 Months	0	0	1	0	Menopause	0	0	1	0
9 Months	2	0	1	0	Carcinoma	1	0	1	0
					Lactating	0	0	1	0
					P.I.D.	0	0	1	0
					Diabetes	0	0	1	0
Total	14	4	18	3		4	0	12	0

negative cases. Table II shows the controls. There were 32 known pregnancies from two to nine months. The seven errors were all subsequently positive. Sixteen negative controls were without error; these tests included males, normal females, menstruating and not menstruating, functional menorrhagia and metrorrhagia, subinvolution (six weeks and two months postpartum), lactation with amenorrhea, normal menopause, pelvic inflammatory disease and diabetes.

TABLE III. CLINICAL TESTS, TWENTY-FOUR HOURS (64)

PREGNANCY	POSITIVE					NEGATIVE			
	5 C.C.		5-20 C.C.			5 C.C.		5-20 C.C.	
	NO.	ERROR	NO.	ERROR		NO.	ERROR	NO.	ERROR
5 Weeks	2	1	1	1	Pos. Preg. 3 wk.	1	0	1	0
6 Weeks	3	0	4	0	Delayed Period	3	0	5	0
7 Weeks	1	0	0	0	Amenorrhea	2	0	4	0
2 Months	3	2	20	4	Lactating	1	0	0	0
3 Months	0	0	2	1	Metrorrhagia	2	0	4	0
Threatened Abortion	2	0	0	0	Menorrhagia	1	0	0	0
					Menopause	1	0	0	0
					Pseudocyesis	0	0	1	0
Total	11	3	27	6		11	0	15	0

Table III includes 64 clinical tests. There were 38 patients who have subsequently been proved pregnant. Of this number 9 results were erroneous but all were correct at a later test. Three patients were five weeks from the last period, the test being performed to confirm suspected pregnancy. Seven tests were made during the sixth week after the last period; in five of these cases the test corroborated clinical findings. The other two cases in the group are of special interest.

One patient did not have a pelvic examination, pregnancy being diagnosed by means of the test alone. The second case was a suspected ectopic pregnancy. Although there was no vaginal bleeding, pain and a small, tender mass in one culdesac as well as a slightly enlarged uterus suggested an extrauterine pregnancy. An exploratory laparotomy was performed and a normal intrauterine pregnancy accompanied by a corpus luteum cyst found. The seven weeks test confirmed the clinical diagnosis. Of the 20 two-month cases, 18 likewise confirmed clinical diagnoses and two deserve comment. In the first instance, the hymen was intact and a satisfactory examination could not be made. The other patient was lactating from a previous pregnancy and had not menstruated since that pregnancy. The two three-months tests were merely confirmatory. Both threatened abortions were during the second month, the differential diagnosis being materially aided by a positive test in each instance.

In the 26 negative clinical tests, pregnancy has definitely been ruled out; there were no errors in this group. In two individuals, pregnancy was suspected because of nausea one week before expected normal menstruation. In each instance the test was negative and the patient had her normal period. Eight cases were done in unexplained delayed periods which varied from two days to two weeks. All of these patients eventually menstruated. Of the 6 amenorrhea cases, 3 are unexplained. The other three were as follows:

Two were definite hypothyroid cases, neither having flowed in several months. The third patient had pulmonary tuberculosis. There were likewise 3 metrorrhagia cases not accounted for, the remaining three being explained in the first instance by subinvolution, in the second by retained products following an abortion, and in the last by a bleeding vessel consequent to a cervical repair. The menorrhagia case was apparently functional. A differential diagnosis between pregnancy and menopause was made by the negative test in the next instance. The pseudocyesis case was in a woman fifty years of age who had not menstruated in six months and claimed she had felt life for several months. The true diagnosis was menopause.

Table IV shows the tests made with the forty-eight hours technic. While the number is comparatively small, it is of importance since Friedman and Lapham report 100 per cent results in 108 tests with this technic.

TABLE IV.   FORTY-EIGHT HOURS FIVE TO TWENTY C.C. (11)*

	NO.	ERROR
Positive Control:		
9 months pregnant	1	0
Negative Control:		
Female menstruating	1	0
Ovarian Cyst	1	0
Menorrhagia	1	0
Clinical Tests:		
6 weeks pregnant	3	0
2 months pregnant	3	0
Delayed period	1	0

*A recent check-up of 100 additional tests showed 97 per cent to be correct.

A comparison of the results obtained with the various technics is shown in Table V. The 5 to 20 c.c. twenty-four hour group shows a correct percentage of 93 per cent if we exclude four errors which we know were due to unsatisfactory test animals.

TABLE V.   CLINICAL TEST AND CONTROL (123)

	NO.	ERROR	CORRECT
All Technics	123	16	87%
5 c.c., 24 hr.	40	7	83%
5-20 c.c., 24 hr.	72	9	88%
5-20 c.c., 48 hr.	11	0	100%

HYDATIDIFORM MOLE AND CHORIONEPITHELIOMA

The behavior of the test in hydatidiform mole and chorionepithelioma is illustrated in Table VI. In the first case, the uterus did not enlarge, normally and a diagnosis of missed abortion was made. Seven months

TABLE VI

HYDATIDIFORM MOLE		CHORIONEPITHELIOMA	
2-11-30	Delivery of normal child	6- 2-29	Last period
6-25-30	Last period	4- 8-30	Hydatidiform mole expelled
12-16-30	Uterus size 3½ mo. pregnant Diagnosis: missed abortion	8-12-30	Pelvic examination negative
1-27-31	Aschheim-Zondek, positive Diagnosis: hydatidiform mole	1-22-31	Uterus Negative Mass ½ inch Adj. to uretha
2- 3-31	Uterus size 4 mo. pregnant	1-28-31	Aschheim-Zondek, positive Diagnosis: chorionepithelioma
2-13-21	Aschheim-Zondek, positive	2-20-31	Aschheim-Zondek, positive
2-15-31	Hydatidiform mole expelled	2-20-31	Died. Cerebral embolus Autopsy: chorionepithelioma Postmortem cath. spec. positive
2-17-31	Fluid aspirated from vesicles Aschheim-Zondek, positive		
2-23-31	7 days postpartum Aschheim-Zondek, negative		
3-15-31	Aschheim-Zondek, questionable		
4- 3-31	Aschheim-Zondek, negative		

TABLE VII. FETAL DEATHS IN UTERO

6- 9-30	Last period
2- 3-31	Aschheim-Zondek positive
2- 5-31	Fetal death
2- 8-31	Aschheim-Zondek negative (Small rabbit)
2-11-31	Aschheim-Zondek questionable, macroscopically positive, microscopically Delivered macerated fetus, hydrocephalic
2-15-31	Aschheim-Zondek negative
6-14-30	Last period
2-23-31	Fetal heart unusually strong
3-10-31	Fetal movement not felt; no fetal heart
3-12-31	Aschheim-Zondek positive
3-15-31	Aschheim-Zondek positive
3-23-31	Aschheim-Zondek positive
3-28-31	Aschheim-Zondek negative
3-29-31	Expelled macerated fetus; true knot in cord
10-15-30	Last period
1- 3-31	Began flowing
2-28-31	Aschheim-Zondek questionable, macroscopically negative, microscopically
3- 5-31	Aschheim-Zondek negative
3-10-31	Aschheim-Zondek negative
3-12-31	Still flowing, uterus small Diagnosis: missed abortion
3-21-31	Bleeding increased, dilatation and curettage Diagnosis: confirmed

after the last period, the uterus was only about the size of a three and one-half months' pregnancy. At this time the test was positive and the diagnosis changed to hydatidiform mole. The diagnosis was confirmed when the mole was expelled one month later. It is of interest to note that a positive reaction was obtained with fluid aspirated from the vesicles of the mole.

The second patient expelled a hydatidiform mole ten months after she stopped menstruating. Pelvic examinations were negative until eight months after the delivery at which time a small mass was palpated adjacent to the urethra. A test performed at this time was positive and a diagnosis of chorionepithelioma made. The patient died one month later and the diagnosis was confirmed by autopsy.

INTRAUTERINE DEATH

The results with death of fetus in utero are shown in Table VII. They are not especially consistent. In the first instance there was a known fetal death. The following day the test was negative, but the correctness of this test is doubtful since the rabbit used was quite small. Three days later the test was questionable. In the second case, the test remained positive for at least thirteen days, but was negative in eighteen days. The last case was one of missed abortion in which the test confirmed the clinical diagnosis.

COMMENT AND SUMMARY

There are but few instances in which an immediate diagnosis of pregnancy is absolutely essential. When such knowledge is of importance, the test is of great value. Ordinarily the forty-eight hour technic is satisfactory and undoubtedly gives the most reliable results. Where speed is the paramount issue, the twenty-four hour test offers close to 90 per cent efficiency.

Great care must be exercised in selection of satisfactory test animals and in the injection of a sufficient amount of urine, especially if the specific gravity is low. It is necessary to be quite cautious when the larger amount of urine is injected intravenously. Occasionally shock will be noted. We have often given 7.5 c.c. at one injection, but find 5 c.c. more satisfactory. The rabbits will tolerate this amount every two hours. We have had only one test animal die from shock. Three other animals died, but in each instance definite putrefaction had taken place in the specimen. This fact emphasizes the necessity of using only fresh urine although we have demonstrated the substance to be active as late as seven days after the specimen had been collected.

Both Friedman and Schneider mention the possibility of a twelve-hour test since it is well known that ovulation takes place in the rabbits in approximately ten hours. We have completed six tests on known pregnancies in this short interval. Four of these were negative, one

questionable and one definitely positive. It is possible that with a more refined technic better results may be obtained with the twelve-hour test.

Our experience with extrauterine pregnancy has been limited to one case. In this instance the test was markedly positive in forty-eight hours and laparotomy revealed a ruptured ectopic.

Where one is dealing with a suspected hydatidiform mole or chorion-epithelioma, the test is of exceptional importance. Again in individuals who have had hydatidiform moles, the tests should be used at regular and frequent intervals since a positive reaction may be the first indication of a beginning chorionepithelioma.

It has been our intention to approach the subject purely from the clinical aspect. Hence we have purposely avoided any discussion of the explanation of the reaction.

CONCLUSIONS

1. Nonpregnant female rabbits at least fourteen weeks old and 1500 gm. in weight are satisfactory test animals for application of the Aschheim-Zondek principle.

2. When a proper amount of urine is injected intravenously in satisfactory test rabbits, the test is reliable in 90 per cent of the cases within twenty-four hours.

3. The modification of the Aschheim-Zondek test, as described, is a valuable aid in the diagnosis of pregnancy, hydatidiform mole, and chorionepithelioma.

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103 MEDICAL ARTS BUILDING

MODIFICATIONS OF THE HORMONE TESTS FOR THE DIAGNOSIS OF PREGNANCY*

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SINCE the introduction of the Aschheim-Zondek test for the diagnosis of pregnancy, in 1928, numerous articles have appeared demonstrating the value of the underlying scientific and theoretical considerations of the test. More recent literature concerning the subject has been centered about simplification of the procedure by the use of rabbits rather than mice. This is due to the fact that there is considerable difficulty in having 5 or 6 immature female mice ready for use. Friedman, in 1929, demonstrated ovulation in rabbits twenty-four hours after the injection of 5 c.c. of urine obtained from a pregnant woman. His method shortened the time required for the performance of the test, demonstrated the practicability of using rabbits, and attained as high a degree of accuracy as Aschheim and Zondek. Schneider in 1931 using rabbits in 100 cases also showed the simplicity of this process over the mice method. Reinhart and Scott, in 1929 confirmed Friedman's work and in May of 1931 altered the test as follows: They perform a laparotomy on the rabbit twenty-four hours after the injection of urine. If no corpora hemorrhagica are present the ovaries are returned and again 5 c.c. of urine are injected into the marginal vein of the ear and the abdomen is again opened twenty-four to thirty-six hours later for a final check.

It is to be noted that in all the rabbit methods described it is advised that the animals should be kept in separate pens from one week (Reinhart and Scott) to three weeks (Friedman and Lapham) before using the rabbits. This complicates the test. In all of these methods the animals are killed or used for other purposes, which increases the cost of performing the test. Schneider mentions the possibility of obtaining a positive reaction in eight to twelve hours after the injection, and where time is an element he advocates using 2 rabbits, killing and examining one at the end of twelve hours.

By using the following method some of the above difficulties to a certain extent are eliminated.

TECHNIC

Supposedly isolated and nonpregnant female rabbits over three months of age and bought directly on the market and kept for ten hours. Immediately before the

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injection of 10 c.c. of morning specimen of urine, the animal is laparotomized, in the Trendelenburg position. The ovaries at this time are examined taking care not to manipulate the organs or their blood supply in order not to produce circulatory artefacts which may subsequently be misinterpreted. The size and color of the ovaries and character of any vesicles, which represent graafian follicles, and the presence and number of any blood follicles are all carefully noted and recorded. If an early pregnancy is present or corpora hemorrhagica found, another animal is used. At intervals of six to twelve hours depending upon the urgency of the case, the abdomen is opened under ether anesthesia. The earliest changes in the ovaries consist in an increase in size and a change in color from a pale yellow to a yellowish

Fig. 1.—Shows the size of ovary from "isolated" rabbit with many follicles and relatively little interstitial glandular tissue. Stains for fat reveal only small isolated foci of lipoids in the interfollicular tissue and very little deposition of lipoid granules in the graafian follicle cells and in the zona pellucida.
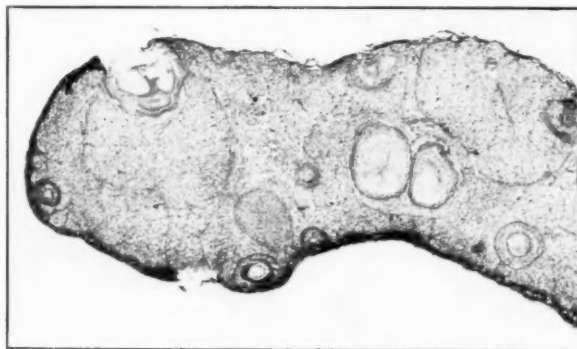

Fig. 2.—Rabbit's ovary five hours after intravenous injection of 10 c.c. of urine from a pregnant patient. Note marked increase in size (compare with Figure 1, of same magnification), the relatively small number of follicles and the enormous widening of the interfollicular spaces due to tremendous deposition of lipoids and increased vascularity.

pale red. In the five-hour specimen demonstrated it is seen that the organ has practically doubled in size following the injection of 10 c.c. of urine from a pregnant patient. If the animal is reopened at the end of twenty-four hours the changes fully described by other authors are seen as in Figs. 2 and 3.

Caution in the administration of ether to the animal is necessary in order not to kill the rabbit by over-saturation with the anesthetic. However, some of the rabbits were given 5 anesthesias within a period of ten hours without any untoward effects. Chloroform and sodium amytal were found unsatisfactory in these experiments.

During the course of the intravenous injection of urine, one of the animals died, after several convulsions. Upon examination of the specimen of urine it was found to contain a large amount of indican.

Upon completion of the test if a "negative" reaction of the ovaries is found, the animal can be used again after thirty-six hours. If the test is "positive" the rabbit can be used again after a period of three weeks.
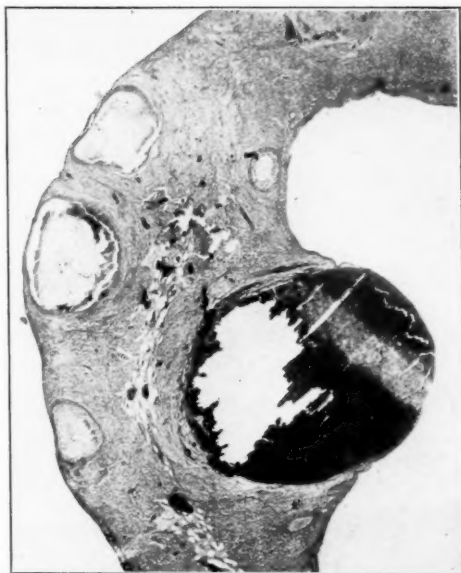

Fig. 3.—Rabbit's ovary twenty-four hours after the injection of 10 c.c. of urine showing two hemorrhagic follicles, same interstitial glandular tissue changes as in Fig. 2, and marked hyperemia of the thecal vessels and interfollicular spaces.

CONCLUSIONS

1. Preliminary laparotomy of rabbits obviates the necessity of keeping the animals for three weeks before performing the test, and enables us to know the exact state of the ovaries before starting the procedure.

2. In order to shorten the period of obtaining a positive reaction for pregnancy in rabbits preliminary and repeated subsequent laparotomies are advised.

3. Laparotomy rather than autopsy of the animals decreases the expense of the test because they can be used repeatedly.

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2400 SOUTH DEARBORN STREET.   *(For discussion, see page 761.)*

A COMPARISON OF THE SEDIMENTATION AND RUGE VIRULENCE TESTS IN 150 GYNECOLOGIC CASES*

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THE standard method of determining the indications and conditions for operation in pelvic inflammatory disease is an history of continued invalidism; a normal leucocyte count and a normal temperature. If an exacerbation of the infection has occurred then a period of at least ten days of normal temperature has to be observed before the chronic inflammatory pelvic lesions are to be attacked surgically.

In late years two laboratory tests have been advocated; namely, the erythrocyte sedimentation test and the virulence test of the cervical secretion. A sedimentation time of less than sixty minutes signifies that the patient cannot be safely subjected to a gynecologic pelvic operation as it indicates the presence of an actively acute infection somewhere in the body. A positive virulence test on the other hand means the existence of pathogenic bacteria of some kind in the genital tract contraindicating operations on the pelvic organs due to the danger of postoperative infections and sepsis.

The purpose of these investigations is to record our observations made in 150 patients of which 132 were subjected to gynecologic operations and in which the safe time of operation was determined by the standard method of the leucocyte count, temperature, history and physical examination. In all these patients the erythrocyte sedimentation time and the virulence tests were done. Thus a comparison could be made between the prognostic efficacy of the older method and the erythrocyte sedimentation time and the cervical virulence test.

TECHNIC

The rate of sedimentation was determined with the aid of the Balachowski sediotessometer. A sterile pipette is rinsed with a 5 per cent neutral potassium oxalate solution. The tip of the finger is cleansed with ether, and blood is drawn into the pipette as is done in making a blood count except instead of drawing the blood with the mouth the squeezing of a rubber hose attached to the top of the pipette creates negative pressure. The pipette which is graduated in millimeters is placed in a stand which has a level regulator and the column of blood is placed at 0 by turning a screw attached to the top of the hose. Readings were recorded at 15, 30, 60, 120 and 180 minutes. A drop of 30 mm. in one hour corresponds to the Linzenmeier method of a drop of 18 mm. in one hour and is considered the dividing line between safe and unsafe operation.

In the Ruge virulence test 5 c.c. of blood drawn from the cubital vein under aseptic precautions is defibrinated by shaking for 5 minutes in a sterile glass tube containing

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glass beads. One half c.c. of this blood is placed in each of two tubes one of which is inoculated with 2 or 3 loopfuls of vaginal or cervical secretion and the other is kept as a control. Smears are made from the contents of both tubes which are immediately thereafter incubated at 37.5° C. Smears are repeated at hourly intervals for three hours and stained with methylene blue. If the organisms increase within three hours the test is positive; i.e., organisms pathogenic for the host are present in the genital canal.

Both tests were done at the same time of the day on the day previous to operation and entirely unknown to the surgeons who were members of the Cook County Hospital gynecologic staff. A vaginal smear, hemoglobin per cent (Talquist), leucocyte and differential counts were done in every patient also the day previous to operation. The duration of the illness, temperature, character of the operation and complications were taken from the history. The diagnosis was taken from the pathologic report.

Of 150 cases examined 132 were operated upon. Among the latter were 29 cases of salpingitis with abdominopelvic operations, 17 cases of uncomplicated myomata with hysterectomies, 7 cases of myomata complicated with salpingo-oophoritis, 12 cases of carcinomata cervicis with radium insertions, 23 cases of other abdominal pelvic pathology with pelvic operations, 33 cases of vaginal pathology with vaginal operations and 11 cases of combined vaginal and abdominal pathology with combined operations.

The salpingo-oophorectomies were divided as follows: (1) Eight cases with a S.T. of 120 minutes or more and without any morbidity or mortality. They also had a negative virulence test. (2) Five cases with a S.T. of 60 minutes or more. Two had stitch infections but negative virulence test. One doubtful virulence test was obtained but without any postoperative complications. (3) Seven cases with a S.T. of 30 minutes or more including one positive virulence test. There were no morbidities or mortalities. (4) Five cases with a S.T. of 15 minutes or more. One had a stitch infection. All had negative virulence tests. (5) Four cases with a S.T. of less than 15 minutes. One patient had a fecal fistula and another a slight temperature for nine days. All had negative virulence tests.

Among the myomata with hysterectomies were 8 cases with a S.T. of 120 minutes or more. Three had a positive virulence test but without any morbidity or mortality. Three cases had a S.T. of 60 minutes or more. All had negative virulence tests and no morbidity or mortality. Two cases had a S.T. of 30 minutes or more. Both had negative virulence tests and were without any morbidity or mortality. Three cases had a S.T. of 15 minutes or more. One of these had a temperature of 100° F. for ten days. Another had a doubtful virulence test but no complications. There was one case with a S.T. of less than 15 minutes and a negative virulence test which developed a rectovaginal fistula.

Among the myomata complicated with salpingo-oophoritis were: One case with a S.T. of 120 minutes or more. Three cases with a S.T. of 60 minutes or more one of which had a temperature of 100° F. for 22 days. Two cases with a S.T. of 30 minutes or more one of which had a stitch

infection. One case with a S.T. of less than 15 minutes and no morbidity. All seven had negative virulence tests.

Of 12 cases of carcinoma cervicis with radium insertions one had a S.T. of 120 minutes or more, a negative virulence test and no complications. One case had a S.T. of 60 minutes or more, a negative virulence test and no complications. Two cases had a S.T. of 30 minutes or more, negative virulence tests and no complications. Four cases had a S.T. of 15 minutes or more. Two of these, one with a positive and one with a doubtful virulence test developed septic temperatures. Four cases had a S.T. of less than 15 minutes. One of these with a positive virulence test died 8 days after the radium insertion from a septicemia. Another case with a doubtful virulence test developed a septic temperature. The other two had negative virulence tests and no complications.

Among 23 cases of other abdominal pelvic pathology with pelvic operations, 8 had a S.T. of 120 minutes or more. All had negative virulence tests and no morbidity or mortality. Two had a S.T. of 60 minutes or more and negative virulence tests and no morbidity or mortality. Nine had a S.T. of 30 minutes or more. Three of these had a positive virulence test one of which developed a slight temperature for 11 days after the operation which was a supravaginal hysterectomy. The diagnosis was fibrosis uteri. Another patient with a negative virulence test died of a pneumonia 3 days after the operation. Three cases had a S.T. of 15 minutes or more one of which had a reactivation of a pulmonary tuberculosis. All had negative virulence tests. There was one patient with a S.T. of less than 15 minutes, a negative virulence test and no complications.

Among 33 cases of vaginal pathology with vaginal operations were 11 cases with a S.T. of 120 minutes or more. Two of these had positive virulence tests but without any complications. One patient with a negative virulence test developed a postoperative pneumonia. Twelve cases had a S.T. of 60 minutes or more with negative virulence tests. There were no morbidities or mortalities in this group. Five cases had a S.T. of 30 minutes or more. One had a positive virulence test. There were no morbidities or mortalities. Three cases had a S.T. of 15 minutes or more. One had a positive and one a doubtful virulence test. The patient with a doubtful virulence test developed a sore throat with pyelitis following the operation. Two cases had a S.T. of less than 15 minutes with negative virulence tests and no complications.

There were 11 cases of combined vaginal and abdominal pathology with combined operations. Three of these had a S.T. of 120 minutes or more, negative virulence tests and no morbidity or mortality. Five cases had a S.T. of 60 minutes or more with one doubtful virulence test. The patient with the doubtful virulence test died of a septic peritonitis 6 days after the operation which was a dilatation, curettage, amputation of the cervix and bilateral salpingectomy with defundation. Three cases had a S.T. of 30 minutes or more. Two had positive virulence tests. One of the latter died of a septic peritonitis 3 days after the operation which was a

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Sturmdorf excision of the cervix, a bartholinectomy and a bilateral salpingectomy.

SUMMARY

Seventy-one patients with a S.T. of 60 minutes or more were operated upon, 4 developed morbidities and there was one death. Sixty-one patients with a S.T. of less than 60 minutes were operated upon with 12 morbidities and 3 mortalities.

S.T.	NO. CASES	NO. MORBIDITIES	NO. MORTALITIES	PER CENT
60 min. or more	71	4	1	7
Less than 60 min.	61	12	3	24.6

In the Ruge virulence test 111 cases were negative with 10 morbidities and 1 mortality. Six cases were doubtful with 3 morbidities and 1 mortality and 15 cases were positive with 3 morbidities and 2 mortalities.

RUGE TEST	NO. CASES	NO. MORBIDITIES	NO. MORTALITIES	PER CENT
Negative	111	10	1	10
Doubtful and Positive	21	6	3	42.8

DISCUSSION

The result of the prognostic evalution of the sedimentation test for the safe time of operation shows that 7 per cent of morbidity and mortality occurred in 71 cases with a S.T. of 60 minutes or more and that 24.6 per cent of morbidity and mortality was seen in the cases with a S. T. of less than 60 minutes. An analysis of the complications following 132 operations shows that four stitch infections occurred: Two in patients with a S.T. of 60 minutes or more, and 2 in patients with a S.T. of less than 60 minutes. A rise in temperature occurred in one patient with a S.T. of 60 minutes or more and a rise in temperature occurred in six patients with a S.T. of less than 60 minutes. There were 2 pneumonias, one in a patient with a S.T. of 60 minutes or more and one in a patient with a S.T. of less than 60 minutes. Septic peritonitis occurred in 2 cases. One had a S.T. of 60 minutes and the other a S.T. of less than 60 minutes. A septicemia, a tuberculosis, a sore throat with pyelitis, a rectovaginal and a fecal fistula occurred in patients with a S.T. of less than 60 minutes. The septicemia was observed in a patient with a group 4 carcinoma. She had a low-grade sepsis before the radium insertion. A reactivation of a pulmonary tuberculosis occurred in a patient who had a bilateral salpingectomy for tuberculous salpingitis. The sore throat with pyelitis occurred 7 days after operation. The rectovaginal fistula occurred during a hysterectomy for fibroids complicated with many firm adhesions. This was purely an accident of surgery. The fecal fistula occurred in a patient who, according to the history, had been ill 7 days, had a temperature of 99.4° F., 13,000 leucocytes and 85 per cent polys. The pathologic report was chronic tubovarian abscess and chronic salpingitis.

In order to correctly evaluate the prognostic efficacy of the sedimentation test it would therefore be necessary to subtract in addition to the carcinomas, the postoperative pneumonias, tuberculosis, sore throat with pyelitis, rectovaginal and fecal fistulas. We would then have the following:

COMPLICATION	S.T. OF 60 MIN. OR MORE	S.T. OF LESS THAN 60 MIN.
Stitch infection	2	2
Temperature	1	3
Septic peritonitis	1	1

or

S.T.	NO. CASES	NO. MORBIDITIES	NO. MORTALITIES	PER CENT
60 min. or more	66	4	1	7.5
Less than 60 min.	49	5	1	12.2

If we make the same correction for the Ruge test as for the sedimentation test the result is as follows:

RUGE TEST	NO. CASES	NO. MORBIDITIES	NO. MORTALITIES	PER CENT
Negative	99	5	1	6
Doubtful and Positive	16	3	1	25

A striking difference in the prognostic efficacy between the sedimentation test and the Ruge virulence test was observed in the carcinomas. There were 8 cases with a sedimentation time of less than 60 minutes. Four of these had a positive or doubtful virulence test. Complications occurred in all four of the latter and in none of those having a negative virulence test.

Had the sedimentation time been used as an indicator for the time of safe operation then 61 of the 132 patients or 46 per cent would not have been subjected to operation. Among the latter not yet mentioned the diagnosis was as follows:

CASE	S.T.	DIAGNOSIS	MORBIDITY	MORTALITY
37	30 min. or more	Adenocarcinoma of corpus	0	0
64	30 min. or more	Ovarian cyst	0	0
74	30 min. or more	Retroversion	0	0
81	30 min. or more	Cystic ovaries	0	0
88	30 min. or more	Retroversion	0	0
97	30 min. or more	Papillary cystadenoma	0	0
148	30 min. or more	Ovarian cyst	0	0
12	30 min. or more	Relaxed vaginal outlet	0	0
65	30 min. or more	3d-degree prolapse	0	0
91	30 min. or more	Relaxed vaginal outlet	0	0
77	15 min. or more	Retroflexion, cystic ovaries	0	0
135	15 min. or more	Ovarian cyst	0	0
39	15 min. or more	Cervical polyp	0	0
146	15 min. or more	Senile vaginitis (dilatation and curettage)	0	0
138	Less than 15 min.	Ectopic pregnancy	0	0

CONCLUSIONS

1. An increase in sedimentation speed of 60 minutes or less was observed in more than 50 per cent of the cases of inflammatory adnexitis, uncomplicated and complicated fibroids and the carcinomata, and in

about 23 per cent of other abdominal and vaginoabdominal pathology not of an inflammatory nature.

2. The presence of virulent organisms is one of the most important causes of postoperative morbidity and mortality but a doubtful or positive virulence test does not depend on the speed of sedimentation.

3. The increase in sedimentation speed is due to some other factor than the virulence of organisms.

4. The sedimentation test is not a reliable guide in the determination of the time for safe operation of adnexal disease.

5. The Ruge virulence test is of value in the prognostication of postoperative morbidity and mortality if the operation takes place at the site of the organisms, usually the cervix.

6. The history, white and differential counts, temperature and physical examination must remain our main guides in the determination of the time for safe operation in adnexal disease, while in cervical and combined cervico-abdominal operations the Ruge virulence test is of undoubted value. A doubtful or positive virulence test contraindicates cervical operations until such a time that the test becomes negative.

THE UNRELIABILITY OF LABORATORY AIDS IN THE DIAGNOSIS OF GONORRHEA IN WOMEN*

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IT IS extremely difficult to secure accurate information regarding the incidence of venereal disease, particularly of gonorrhea. Despite the recognized greater prevalence of gonorrhea, only 8840 cases were reported to the New York City Health Department during the year 1929, an incidence of 0.2 per cent, while 23,772 cases of syphilis were reported during the same period, an incidence of 0.5 per cent.

In an effort to secure information of a more definite character, Brunet[1] endeavored to determine the number of cases of venereal disease under treatment on a specific date by circulating an appropriate questionnaire addressed to every physician and the various institutions in the City of New York. Replies were received from 9920 physicians and 161 institutions. Only 5259 physicians and 98 institutions reported cases under treatment on that date; 4661 physicians and 63 institutions reported that they had no cases under treatment at that time.

The total number of cases of syphilis acknowledged by these agencies was 29,423, an incidence of 0.5 per cent. The total number of cases of gonorrhea was 23,861, an incidence of 0.4 per cent. These figures are somewhat better than those reported to the Health Department, but it

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*From the Venereal Disease Service, Department of Health, City of New York.

is still evident that the reported cases of syphilis outnumber those of gonorrhea. Only 5660 females were reported under treatment for gonorrhea as compared with 18,201 males, and 10,810 females under treatment for syphilis. The much smaller number of females having gonorrhea is striking, and the explanation of such a wide discrepancy undoubtedly lies in the fact that the majority of cases are diagnosed by the laboratory technician.

In an effort to assay the justification for this practice, a detailed study of the results of the examinations of women convicted of various offenses, mainly prostitution, during the past eleven years, was undertaken. These examinations were made at the various City prisons, the majority at Jefferson Market. In this group of women in whom venereal diseases are apt to be prevalent, no general idea of incidence can be obtained, but the opportunity for the study of the diseases themselves is unusual. All blood and smear specimens were submitted to the Health Department laboratory for examination. Smears were always taken from the urethra and cervix, and when indicated, from other suspicious locations. All smears were stained by Gram's method.

In Tables I and II the figures for 1925 to 1929 inclusive are given separately so that the statistics of the last five years with the total may be compared, but only the eleven-year figures are mentioned in the discussion. The total number of women examined from 1919 to 1929 was 21,610. Of this number 10,932 or about 50 per cent were found to be infected. Gonorrhea was diagnosed clinically in 6425 cases, or 59 per cent of those diseased. It is interesting to note in comparison the 5,660 women reported as having gonorrhea out of 16,470 women diseased, or 35 per cent, as reported in Brunet's questionnaire.

TABLE I. THE EXAMINATION OF CONVICTED WOMEN TO DETERMINE THE INCIDENCE OF VENEREAL DISEASE

	1919-1929	1925-1929	PER CENT OF TOTAL EXAMINED		PER CENT OF NO. INFECTED	
			1919-1929	1925-1929	1919-1929	1925-1929
Total number examined	21,610	11,479				
Number with no evidence of venereal disease	10,675	5,912				
Number having venereal disease	10,932	5,567	50	50		
Gonorrhea diagnosed clinically	6,425	3,083	30	30	59	55
Number with smear positive for gonococci	796	444	4	4	7.5	8

TABLE II. RESULT OF SMEAR EXAMINATION IN CONVICTED WOMEN HAVING GONORRHEA

	1919-1929	PER CENT	1925-1929	PER CENT
Total number with gonorrhea diagnosed clinically	6425		3083	
Positive smear in cases clinically diagnosed	460	7	230	7
Positive smear in cases undiagnosed clinically	336		214	
Total number of positive smears	796	13	444	14
Undiagnosed cases with positive smear, added to those diagnosed clinically	6761	12	3297	13.5

SMEAR EXAMINATION

The total number of positive smears found in our cases was 796 or about 4 per cent of the total number examined.

It is clearly evident that the smear examination detects only about one-seventh to one-eighth of the gonococcal infection in women that can be diagnosed by clinical means. It should be remembered in this connection that these percentages represent the results of a single smear examination. The taking of a single smear corresponds to the usual custom of the physician in private or institutional practice when seeking laboratory aid in arriving at a diagnosis. Furthermore, many physicians do not regard a smear as positive unless gram-negative intracellular diplococci are present. No account is taken of the fact that gonococci occur extracellularly as well as intracellularly, and that their characteristics vary, depending on their age, in size and staining qualities. Again, the majority of patients harbor old, chronic infections. The gonococci rapidly disappear from the surface secretions, but one evidence of infection, namely, the pus cell, remains. In order to derive material aid from the examination of smears, more than one smear must be taken. Gram stain, when used in conjunction with the clinical examination, is unnecessary; methylene blue is simpler and equally satisfactory. The smear that does not show typical intracellular gonococci, but does show extracellular diplococci, or atypical intracellular cocci, or the smear that shows nothing but pus cells, should be interpreted in the light of the clinical evidence present. Obviously, the several details are best correlated by the physician who examines the patient. Even when all this is taken into consideration, the smear examination furnishes but meager aid in establishing the diagnosis of gonorrhea in women.

EXAMINATIONS OF CULTURES

Cultures of the gonococcus afford but little additional help. They should only be undertaken in a well-equipped laboratory, manned by ex-

pert technicians.   Torrey, Wilson, and Buckell[2] working in a group of
the same type of patients, with the most careful technic, obtained only
28.4 per cent positive cultures.   Aside from the difficulty of growing the
organism, and the necessity for special media of definite acidity and
temperature, failures are numerous, since the other organisms present
under the same cultural conditions rapidly overgrow the gonococcus.
Even when a growth is obtained and transplanted, and regrown in pure
culture, it cannot be identified by smear.   Nothing but gram-negative
diplococci are present, and inasmuch as there are no pus cells, the
diagnosis cannot be made.   It therefore becomes necessary to study the
action of the organism on the various sugars to make a differential
diagnosis.   This involves the lapse of at least five days before a report
can be rendered.   Under these circumstances, culture certainly becomes
impractical for a routine diagnosis.

GONORRHEA COMPLEMENT FIXATION TEST

The blood test in gonorrhea is a specific complement fixation test, in
that killed gonococci are used as the antigen.   The blood test in syphilis
is not a specific complement fixation test, because nonsyphilitic material,
such as beef heart, is used as the antigen.   Theoretically then, the comple-
ment fixation test for gonorrhea should be as accurate or more so than
that for syphilis.   Whether or not this is actually true, may be readily
determined from the following discussion.

In discussing the complement fixation test in convicted women, only
the figures for 1925 and 1926 are available.   Out of a total of 2,795
cases examined, 55, or about 2 per cent, gave a positive complement fixa-
tion of 2-plus or over.   If one should include the doubtful and 1-plus
tests, a total of 243 or 9 per cent could be considered positive.   Of the
total number examined, 1041 were diagnosed as having gonorrhea on
clinical evidence.   In this group, only 28 or 2 per cent had a 2-plus,
or over, fixation.   Including the doubtful and 1-plus fixations, 113 or
10.8 per cent would be considered positive.   At the same time, of the
1,754 cases in which no diagnosis could be made, clinically, 27 or 1.5
per cent had a 2-plus, or over, fixation, and adding the doubtful and
1-plus fixations, a total of 130 or 7.5 per cent were reported as having
some degree of fixation.   Assuming that these 130 cases in which fixation
occurred were missed in clinical diagnosis and added to the 1,041 which
were clinically diagnosed, the total of 1,171 clinical cases having 243
fixations of some degree would still be only 20.5 per cent.

It is unquestionably a dangerous practice to base a diagnosis of
gonorrhea on a doubtful or 1-plus fixation.   Yet even under the most
liberal interpretation, a totally inadequate percentage of positive re-
sults are obtained.   Since 1927 the routine examination of blood speci-
mens for complement fixation reactions for gonorrhea in New York City
court cases has been abandoned.

TABLE III. RESULTS OF COMPLEMENT FIXATION TESTS FOR GONORRHEA IN CONVICTED WOMEN

	1925-1926	PER CENT OF TOTAL NUMBER EXAMINED	PER CENT OF NUMBER HAVING GONORRHEA	PER CENT OF NUMBER FREE FROM GONORRHEA
Total number examined	2795			
Positive complement fixation 2-plus or over	55	2		
Complement fixation, including doubtful and 1-plus	243	9		
Number clinically diagnosed as gonorrhea	1041			
Complement fixation 2-plus or over in clinical gonorrhea	28		2	
Complement fixation, including doubtful and 1-plus in clinical gonorrhea	113		10.8	
Number clinically negative	1754			
Complement fixation 2-plus or over in negative cases	27			1.5
Complement fixation, including doubtful and 1-plus in negative cases	130			7.5
Negative cases with some degree of fixation added to cases diagnosed clinically	1171			
Total with some fixation	243		20.5	

TABLE IV. RESULT OF COMPLEMENT FIXATION TESTS FOR SYPHILIS IN CONVICTED WOMEN

	1925-1929
Total number examined	11,479
Positive complement fixation test 2-plus or over	2,914
Percentage positive of total examined	26

The blood examinations for syphilis in the cases examined at the court from 1925 to 1929 showed 2,914 positive fixations of 2-plus or over out of a total of 11,479 cases, or 26 per cent. Here, again, one notes the greater percentage of positive reports in a disease which is far less frequent than gonorrhea.

Additional information regarding the relative value of the blood test for syphilis and gonorrhea may be obtained by comparison of the results in the routine examination of blood specimens submitted to the labora-

TABLE V. RESULTS OF ROUTINE EXAMINATION OF BLOOD SPECIMENS FOR
SYPHILIS AND GONORRHEA

	SYPHILIS 1925-1929	GONORRHEA 1925-1929
Total number examined	581,112	45,844
Total positive complement fixation test 2-plus or over	81,507	1,068
Percentage positive	14	2
Total doubtful and 1-plus fixations		3,011
Percentage doubtful fixations		6.5
Percentage positive plus doubtful fixations		8.5

tory in the past five years. There were 581,112 specimens submitted for the Wassermann test, of which 81,507, or 14 per cent, showed a 2-plus or over, fixation. During the same period, 45,844 specimens were examined for gonorrhea, of which 1,068, or 2 per cent, showed a positive fixation of 2-plus or over. Even when adding the 3,011 doubtful cases, and considering the entire 4,079 cases as positive, the percentage would be only 8.5. This comparison further emphasizes the unsatisfactory percentage of positive results obtained in the examination of blood for gonorrhea. It is difficult to understand the uncertain results of the blood fixation test in gonorrhea. One must assume either that no antibodies are produced in this disease, or else that the antigen is at fault. Repeated experiments with many kinds and proportions of antigen have failed to improve the number of positive results. Investigations along these lines still continue, and it is possible that ultimately a more reliable technic will be evolved.

CONCLUSIONS

From the foregoing discussion, the following comments concerning laboratory procedures and their value in the diagnosis of gonorrhea in women seem justified:

1. Repeated smears should be taken and carefully examined.

2. The use of Gram's stain is not essential. In conjunction with a proper evaluation of the clinical examination, the methylene blue stain is adequate for practical purposes.

3. A positive smear is conclusive evidence of infection.

4. A negative smear, even when repeated, does not exclude the presence of a gonococcal infection in women.

5. Suspicious organisms, extra- or intracellular, should be interpreted in accordance with the clinical evidence.

6. Pure spreads of pus cells, even without organisms present, should be regarded as suspicious evidence of gonococcal infection.

7. When cultures are taken and prove positive, they constitute conclusive criteria, but are not practical or well adapted to routine practice.

8. A negative culture does not exclude the presence of a gonococcal infection.

9. The complement fixation test for gonorrhea with the present technic is unreliable. Neither positive nor negative findings are conclusive.

10. Unless an improved technic affording more reliable results is evolved, the fixation test should not be used for the diagnosis of gonorrhea or for the control of its treatment.

Even under the most favorable conditions, it is apparent that laboratory procedures are of minor importance in establishing a diagnosis of gonorrhea in women. A wider appreciation of this fact, with a consequently greater reliance upon the history and clinical evidence, will suggest the correct diagnosis in many of the now unrecognized cases of gonorrhea in women.

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151 WEST SEVENTY-SEVENTH STREET.

SOME OBSERVATIONS CONCERNING ERYTHEMATOUS ERUPTIONS SIMULATING SCARLET FEVER DEVELOPING IN THE PUERPERIUM*

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A REVIEW of the literature yields a wide divergence of opinion as to the etiology of scarlet-like eruptions developing in the puerperium. Williams[1] in his text book of obstetrics discusses this problem at some length. Schamberg and Kolmer[2] gave numerous essential points in the differential diagnosis of scarlet fever from puerperal sepsis with a scarlatiniform rash. These scarlatiniform eruptions may be associated with severe constitutional reactions with the clinical picture of sepsis accompanied by high mortality; or, they may be mild in character associated with but little constitutional reaction, frequently diagnosed clinically as toxic erythemas. Of late, particularly on the Continent, an attempt has been made to determine the susceptibility of pregnant women to puerperal infection with the streptococcus by the determination of the susceptibility to Dick's toxin. So far, the results of this study have been of little clinical value. In France Blaize and Mayer,[3] and De Lavergne and Fruhinsholz[4] have, at comparatively recent date, discussed these erythematous eruptions developing subsequent to childbirth, concluding that they may develop as a complication of sepsis, or that they may be benign in character, being merely the cutaneous manifestation of some unknown constitutional toxemia.

During the past seven years eight women, early in the puerperium, suffering from a scarlet eruption that could not be clinically differentiated from scarlet fever, have been received by the contagious service of the Kansas City General Hospital. In all these cases the throat symptoms, so characteristic in the onset of scarlet fever, were extremely mild or completely absent. While the mucous membrane of the entire oral cavity was red in appearance and some degree of sore throat was present, the throat symptoms, if present, were extremely mild and the characteristic adenopathy under the angle of the jaw was wanting. In four of these cases death occurred. Two cases came to necropsy. In the terminal 24 hours great abdominal distention was present, and in the two cases that came to autopsy, the clinical and postmortem findings were such that we must accept the fact that the infection occurred from below. Two of these patients, presenting a scarlet-like eruption which developed subsequent to childbirth, were treated by the administration of Dick's antitoxin. In one instance the therapeutic response was so brilliant that there is no question, in our judgment, as to the therapeutic efficiency of this procedure. In the second case, to be recorded in detail, the eruption was blanched and considerable symptomatic improvement occurred 24 hours subsequent to the administration of the serum. Death occurred, however, on the fourth hospital day, with extreme abdominal distention and the clinical picture of a generalized peritonitis.

In the face of these observations made over a period of years in a contagious hospital, we gained the impression that most cases of scarlet fever in the puerperium were in reality puerperal sepsis. The description that follows is in absolute accord with our clinical impressions of the five preceding cases. On November 11, 1930, opportunity for further study of this question presented itself in the following case:

Patient admitted to the contagious service of the Kansas City General Hospital, November 11, 1930, a multipara 4, age thirty-two, who denied ever having had scarlet fever. At the time of admission the rectal temperature was 104°, pulse 120. Four days prior to admission the patient gave birth to a normal child. The onset of the present illness was abrupt—two days subsequent to the birth of the child—with chills and severe back pain; 48 hours later a diffuse scarlet eruption developed similar to that seen in scarlet fever. The examination of the nose and throat was negative and the history of the antecedent sore throat, so characteristic in scarlet fever, was wanting. Two hours subsequent to the patient's admission to the hospital, 20 c.c. of Dick's antitoxin was administered, subsequently the eruption was markedly blanched. However, the abdomen became markedly distended and death occurred on the fourth hospital day. Blood culture was positive, but the growth was not apparent until several days after the necropsy. The following facts are extracted from the autopsy report of Duncan and De Groat:

"The body is that of a rather large, well-developed, well-nourished white woman about thirty-five years of age. There is a marked cyanosis of the skin over the entire body. The external jugular veins are dilated. The abdomen is enormously distended. Both lungs lie free in their respective cavities. The lower portion of the right lung is of a deep red color, is firm, crepitation is markedly reduced. From the cut surface exudes a large amount of bloody fluid. The left lung shows no changes other than a moderate amount of hypostatic postmortem congestion.

"The pericardial sac contains about 150 c.c. of a clear, straw-colored fluid. The heart is large and dilated. The myocardium has a markedly scalded appearance. No changes are noted in the valves, which are all smooth and flexible. The blood has a watery brownish appearance.

"The peritoneal cavity contains about 3 quarts of straw-colored fluid. The intestines are enormously distended. The peritoneal fluid is cultured. The intestinal tract is otherwise normal.

"The spleen is large and soft. It has a deep red color. The capsule is smooth.

"The uterus reaches within 2 cm. of the umbilicus. It is very large and soft. The pelvic cellular tissue is extremely edematous. The uterus and bladder are removed *en bloc*. The wall of the uterus is extremely soft and edematous. The endometrium is everywhere hemorrhagic, and in places is covered by a soft grayish exudate. Cultures taken from it show a long chain streptococcus—hemolytic in type."

Subsequent to the necropsy De Groat stained several sections from the uterus and was able to demonstrate streptococci underneath the uterine mucosa. De Groat's histologic report follows:

"Sections taken from the endometrium show extensive necrosis, the glands of the mucosa having almost entirely disappeared. The myometrium is extremely edematous, and scattered through it are moderate numbers of polymorphonuclear leucocytes. The changes in the uterus are particularly marked in the region of the cervix. Throughout the wall there are numerous foci of polymorphonuclear leucocytes. In some of the veins thrombosis has occurred. These thrombi are suppurating.

"Gram stains of the uterus and parametrium show innumerable long chain streptococci in the necrotic endometrium. No organisms can be discovered in the deeper tissues."

From the history and the lack of upper respiratory symptoms, the postmortem findings of generalized peritonitis and the staining of the streptococci in the uterine wall, associated with a positive blood culture, we were convinced that this was a case of puerperal sepsis with a streptococcus similar, if not identical, to Dick's streptococcus scarlatina. The specimen of streptococci was forwarded to Dr. Cornelia M. Downs of the Department of Bacteriology, University of Kansas at Lawrence, for study.

The organism, isolated in pure culture from the blood of the patient, was a long chain, gram-positive hemolytic streptococcus. It gave typical hemolysis of the beta type in poured rabbit and human blood agar plates. Culturally it fermented dextrose, lactose, salicin, but not mannit or inulin. It would be classified therefore as a variety of Streptococcus pyogenes.

It was thought that it might be of some interest to test out the ability of this strain to produce an extracellular toxin which might give a skin test similar to that of Dick toxin and many other hemolytic streptococci. The organism was cultivated for 48 hours in a 0.5 per cent dextrose-meat infusion broth. This was passed through a Berkefeld filter, tested for sterility, and 0.5 per cent phenol added as a preservative. Similar toxins were prepared from culture No. 40, a hemolytic streptococcus of the beta type from a fatal case of endocarditis. Also filtrates from a hemolytic streptococcus of the beta type No. 57 cultured from a case of

TABLE I*

As a preliminary titration *6 known Dick positive* individuals responded as tabulated to the filtered toxin of the streptococci under investigation.

Commercial Dick's toxin	+	+	+	+	+	+
Laboratory strain No. 40. Cultured from a fatal case of endocarditis.	—	—	—	—	—	—
Laboratory strain No. 57. Cultured from scarlet fever obtained from New York Board of Health.	+	+	+	+	+	+
Laboratory strain No. 334. Obtained by blood culture from fatal case of puerperal sepsis under discussion.	+	+	+	+	+	+

*This table is compiled from the cutaneous reactions to a 1:1000 dilution of the filtered exotoxin. Filtrate No. 40 gave slight redness only. Strains 57 and 334 produced definite erythema of above one centimeter when injected intradermally.

scarlet fever. This culture was obtained through the kindness of Dr. Mary Kirkbride, New York State Board of Health.

A group of forty-seven individuals were subjected to the intradermal injection with Dick toxin, the filtrate from culture No. 334, and the filtrate from culture No. 40. The reactions to these exotoxins is recorded in Table II.

TABLE II

CASES	COMMERCIAL DICK TOXIN	FILTRATE NO. 334	FILTRATE NO. 40
5	+	+	+
2	+	+	—
1	+	—	—
5	—	—	+
34	—	—	—

The results obtained in this series of forty-seven cases were widely divergent from the cutaneous response to the original six Dick positive individuals whose reactions are recorded in Table I. For this reason a series of fifty-five students were injected intradermally with commercial Dick toxin and the filtrate from culture No. 334. The results of this observation are recorded in Table III.

A study of Table III shows that twenty-nine individuals gave an erythema in response to the intradermal injection of a streptococci exotoxin. Twenty-six showed no reaction. Of the twenty-nine reactors,

TABLE III

CASES	COMMERCIAL DICK TOXIN	FILTRATE NO. 334
15	+	+
10	+	—
4	—	+
26	—	—

Dick's toxin and the filtrate from culture No. 334 agreed in behavior in fifteen cases. However, ten cases responded to Dick's toxin, but failed to react to filtrate No. 334. Four cases reacted to filtrate No. 334 and were negative to Dick's toxin. Dilutions of 1:1000 were used throughout this series.

Further studies were pursued on a series of twenty-seven individuals. In these cases a dilution of 1:500 of the filtrate from culture No. 334 was used. Also 1:500 dilution of Dick's toxin and a 1:500 dilution of the toxin from strain No. 57 received from the New York Board of Health. Controls were used in all cases using toxin from the respective cultures boiled ten minutes and allowed to cool at room temperature. The results of this observation are recorded in Table IV.

TABLE IV

CASES	COMMERCIAL DICK TOXIN	FILTRATE NO. 334	FILTRATE NO. 57
7	+	+	+
2	+	—	+
2	—	+	+
6	—	—	+
10	—	—	—

A study of the above table reveals an equal number of reactors to Dick's toxin and to the toxin obtained from the streptococcus grown from the blood of the case of puerperal sepsis under discussion. However, the exotoxin from the scarlet fever-producing streptococcus gave more positive reactions than the filtrate No. 334 or Dick's toxin. Controls using the boiled toxin gave a high incidence of reactions. Whether this was due to the hypersensitivity to some substance contained in the broth or to the bacterial protein or to a heat-stable toxin could not be determined. The presence of the preservative is a factor to receive consideration. The degree of redness produced by heated toxin controls was very minor in comparison to a positive cutaneous reaction. Ando[5] has shown that scarlet fever toxin is very complex, containing heat-stable toxins and if the crude filtrate is used, bacterial proteins to which the skin may be reactive. The Dick toxin used was a commercial preparation and gave very few reactions when heated. Wheeler,[6] Kirkbride and Wheeler,[7,8] Williams,[9] and others have shown that many of the hemolytic streptococci produce toxic substances which will give reactions in human skin. These reactions may be neutralized by scarlet fever antitoxin. The skin test, therefore, cannot be used as a means for the identification of a scarlet fever strain. It is also generally agreed that agglutination tests do not give a satisfactory means of identifying the streptococci. It is of interest to note in this series of 135 individuals subjected to intradermal injections with 4 streptococci exotoxins, that the number of Dick positives was 35.5 per cent. The number of No. 334 positive was 30.4 per cent. These

figures are in quite close agreement with those of Zingher,[11] Zoeller,[12] Sherwood,[13,14] and others.

From the above results we may conclude that we are dealing here with a streptococcus which will produce toxin giving skin reactions similar to the Dick test and which will produce a rash clinically which is blanched by Dick antitoxin.

CONCLUSIONS

1. It is obvious that scarlet fever may attack a woman in the puerperium; however, in our experience, scarlet fever developing in the puerperium is puerperal infection with a streptococcus whose exotoxin is capable of producing an erythematous eruption. This particular streptococcus may invade the blood stream and produce the clinical course of puerperal sepsis with a high mortality. The infection may be confined to the uterus, the constitutional reaction being slight, and the associated erythematous eruption is due to the absorption of the erythema-producing exotoxins. The prognosis in this group of cases is excellent.

2. The rôle of Dick's streptococcus scarlatina in the production of puerperal infections, associated with erythema, cannot, in our judgment, be definitely established. However, the exotoxin elaborated by a streptococcus grown from the blood of women suffering from puerperal sepsis, associated with an exanthem that could not be differentiated from scarlet fever, would produce a characteristic reaction in Dick-positive individuals. The behavior of this exotoxin in Dick-positive individuals did not agree in every case. The agreement in behavior, Dick's streptococcus scarlatina, was so closely associated that biologic differentiation is not possible.

3. Exotoxins from the streptococcus that produce erythematous eruptions simulating scarlet fever in the puerperium are neutralized by Dick's antitoxin.

4. The therapeutic efficiency of the antitoxin is in direct ratio to the exotoxin elaborated. Neutralization of this erythema producing exotoxin of streptococcic origin may be of great therapeutic importance.

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902 ARGYLE BUILDING.

THE EFFECT UPON THE NEWBORN CHILD OF SODIUM ISO-AMYLETHYL BARBITURATE (SODIUM AMYTAL) WHEN USED AS AN OBSTETRIC ANALGESIC AND ANESTHETIC

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THIS study is undertaken to determine whether or not the use of sodium amytal in obstetrics has any harmful effect upon the newborn child.

Morehead and Mussey[1] noted no respiratory embarrassment in normal babies delivered with the aid of sodium iso-amylethyl barbiturate. Massey[2] noted that the babies of mothers given this drug seemed unaffected. Jaeger,[3] in discussing the use of sodium iso-amylethyl barbiturate in cesarean section, mentions that the baby was in about the same state when delivered as when hyoscine, morphine, and cactin were used in twilight sleep. Moore[4] reports the use of this drug in 4 cases of eclampsia. All babies included in these case reports were small, ranging in weight from 3.75 to 5.66 pounds, but were reported to be in excellent condition and all did well. Robbins, McCallum, Mendenhall and Zerfas[5] reported 80 babies studied in detail following deliveries in which sodium iso-amylethyl barbiturate anesthesia was used. Of this group 3 were asphyxiated and respiration was started with more or less difficulty; 2 were apneic, and the remainder began breathing with little or no difficulty. Thirty of these babies showed an average weight loss of nine ounces occurring over an average period of three and a half days. Birth weights were regained in an average of eight and a half days. One stillbirth was reported, cause undetermined. They conclude that danger to the child has not been proved. Boucek and Renton,[6] in a recent experimental study on white rats, found that the amount of sodium iso-amylethyl barbiturate necessary to anesthetize a pregnant rat did not in any way interfere with the viability of the fetus; the fetus was not anesthetized and readily responded to gross stimulation.

One hundred and forty-nine newborn babies, together with their mothers, collected over approximately a year's time, make up this series.* Seventy-eight of these mothers received sodium iso-amylethyl barbiturate either orally or intravenously. Of these, 53 received morphine and hyoscine, while 5 received only morphine preceding or together with, the sodium iso-amylethyl barbiturate. Included in this group were 45 primiparae; the rest were multiparae, including 6 who had gone through two or more pregnancies. Seventy-one of the mothers received no sodium iso-amylethyl barbiturate. Of this group 40 received morphine and hyoscine, and 5 received only morphine during labor. There were 37 primiparae, and 14 multiparae who had gone through two or more previous pregnancies.

All infants in this series received a physical examination by a pediatrician within a few hours after delivery. If there was any question as to a child's condition, it was seen immediately. A routine feeding of half

*These patients were all delivered on the obstetric service of Dr. J. W. Bourland and by his kindness the material was obtained.

TABLE I

GROUP	GRAVIDA			MORPHINE AND HYOSCINE	MORPHINE	TIME IN HOSPITAL BEFORE DELIVERY		AVERAGE TIME IN HOSPITAL BEFORE DELIVERY	AVERAGE TIME SODIUM AMYTAL WAS GIVEN BEFORE DELIVERY	AVERAGE DOSE SODIUM ISO-AMYLETHYL BARBITURATE
	I	II	III OR MORE			MAX.	MIN.			
No sodium iso-amylethyl barbiturate	37	20	14	40	5	24 hr.	30 min.	6.3 hr.		
Sodium iso-amylethyl barbiturate orally	27	12	4	30	2	32 hr.	3 hr.	11.2 hr.	3.75 hr.	0.53 gm.
Sodium iso-amylethyl barbiturate intravenously	28	5	2	23	3	20 hr.	2 hr.	8.8 hr.	2.9 hr.	0.69 gm.

strength skimmed milk with 5 per cent added dextrimaltose was offered every three hours, beginning eight hours after delivery. This feeding was continued only until the mother's breast milk appeared. Additional water was given. All babies were weighed daily. If breast feeding failed to produce a satisfactory gain in weight, supplementary feedings of various cow's milk mixtures were offered. The majority of the babies remained under observation in the hospital for approximately fourteen days.

The mothers were divided into groups, depending upon whether they received no sodium iso-amylethyl barbiturate or were given the drug either orally or intravenously, as shown in Table I. In this table also appears data pertaining to the amounts and time of administration of the drug.

It will be noted that the time of administration varied considerably. As previously mentioned, a considerable number received morphine and hyoscine, or morphine alone. Usually it was a routine practice to give these drugs early in the first stage of labor. If the pain was controlled satisfactorily, no other medication was used. The patients given sodium iso-amylethyl barbiturate orally, received the drug in from 0.18 to 0.36 gram doses, repeated as necessary, depending upon the severity of the pain. The time of beginning the oral administration varied from thirteen hours to forty-five minutes before delivery and the total dose varied from 1.62 to 0.18 grams. When sodium iso-amylethyl barbiturate was given intravenously, much the same procedure was followed, except that an effort was made to wait until the first stage of labor was nearly completed. The time of beginning intravenous administrations varied from seven hours to twenty minutes before delivery, and the total dose varied from 1.35 to 0.45 grams. A few patients received the drug both orally and intravenously. These are classified with the latter group. It should be mentioned that nearly all patients received nitrous oxide anesthesia during the actual delivery.

The babies are grouped in the same manner as the mothers, as shown in Table II. This table also includes the maximum, minimum, and average figures for birth weight, initial weight loss, and the time required to regain the birth weight.

There is little difference to be observed in the average figures of these groups. Of the babies delivered without the use of sodium iso-amylethyl barbiturate, 2 were slightly asphyxiated; 1 had symptoms of thymic enlargement which were confirmed by roentgen ray examination; it became symptom-free following roentgen ray treatment. Eighteen of this group required supplementary feeding. In the group delivered with sodium iso-amylethyl barbiturate anesthesia, administered either orally or intravenously, there were 3 babies slightly asphyxiated; 2 with symptoms of thymic enlargement, confirmed and treated as previously noted; 1 had a moderately severe intestinal hemorrhage; 14 of the group required sup-

TABLE II

| GROUP | TOTAL NO. CASES | MALES PER CENT | BIRTH WEIGHT | | AVERAGE BIRTH WEIGHT | INITIAL WEIGHT LOSS | | AVERAGE WEIGHT LOSS | AVERAGE DAYS WEIGHT LOSS OCCURRED | AVERAGE TIME BIRTH WEIGHT REGAINED |
			MAX.	MIN.		MAX.	MIN.			
No sodium iso-amylethyl barbiturate	71	45	4659 gm.	2500 gm.	3410 gm.	690 gm.	90 gm.	230 gm.	3.08 days	12.1 days
Sodium iso-amylethyl barbiturate intravenously	34	50	4845 gm.	2500 gm.	3437 gm.	450 gm.	120 gm.	225 gm.	3 days	11.03 days
Sodium iso-amylethyl barbiturate orally	44	61	4432 gm.	2227 gm.	3380 gm.	420 gm.	120 gm.	240 gm.	2.8 days	12.8 days

plementary feeding. In both groups there was an occasional complaint that the baby was aroused with difficulty at nursing time and nursed poorly. This occurred during the first three to seven days, about equally in the cases that had, and had not, received sodium iso-amylethyl barbiturate, and soon corrected itself. It has been possible to follow up a certain number of these babies for varying periods of time up to the eighth month. All are developing normally.

In conclusion, it appears that, in accord with other reports in the literature, sodium iso-amylethyl barbiturate has no injurious effect on the newborn child when given in the customary doses as an obstetric analgesic or anesthetic.

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4105 LIVE OAK STREET

BACTERIOLOGY OF NEWBORN WITH SPECIAL REFERENCE TO HEMOLYTIC STREPTOCOCCI

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HEMOLYTIC streptococci have been found in cultures taken from the throats and tonsils of normal children[1] and adults.[2] However, little has been done to determine the incidence of beta (B) hemolytic streptococci in the bacterial flora of infants' throats. With this object in mind, a study was made to determine whether or not infants' throats were sterile at birth; when the mouth cavity became inhabited by bacteria; the type of streptococci present, with special reference to the beta hemolytic type of Smith and Brown[3]; and finally to determine the incidence of hemolytic streptococci in normal infants' throats compared with that of adults.

According to Campo[4] the mouth of the fetus is sterile, and Pasteur[4] states that all the cavities of the fetus are sterile. It was of interest to find how soon, and with what type of organisms, the mouth cavity became invaded. Bonnaire and Keim,[5] in 1900, found the mouth sterile several hours after birth, but demonstrated diplococci in the throat of one child twenty-four hours old. Streptococci were not present in infants on direct examination of swabs. The work of Bonnaire and Keim was of no assistance in determining whether or not hemolytic streptococci were present, as to the differentiation of hemolytic streptococci on blood agar was introduced by

Schottmüller[6] in 1903. They state that suckling increased the number of species of organisms while the number of individual organisms in each species diminished.

Mme. Brailovsky-Lounkevitch[7] in 1915 examined several infants from birth to several days of age and found the mouth liquid absolutely sterile at birth. She confirmed the work of Jeannin,[7] who, in 1904, reported that the buccal cavity commenced to populate itself about the sixth hour. At the tenth hour she demonstrated the organisms on direct examination of the mouth liquid. The numbers increased very rapidly after the tenth hour. Jeannin demonstrated species of staphylococci soon after birth. Bacillus coli was found nine hours and streptococci twelve hours after birth. Lounkevitch states that the Streptococcus salivarius assumes an important place by the tenth day and is constant during the first year, whereas other bacteria of the air have a tendency to disappear. Only one child had Streptococcus pyogenes in the throat at the tenth hour.

Bloomfield,[8] in a series of 18 infants, reported that cultures taken before the twelfth hour revealed no organisms, except in one infant who had green streptococci. A profuse growth appeared when nursing started. The infants' throats contained Staphylococcus albus in 50 per cent of the cultures; Staphylococcus aureus was rarely found and was not constant. Streptococci, which formed small, green-producing, gray colonies, were present within twenty-four hours. The latter were found in the throats of attendants. Only one infant had the beta hemolytic streptococcus and this was found on two occasions. Bloomfield stated that nonhemolytic streptococci were present because they have adapted themselves to the mucous membranes of the upper air passages. He concluded that hemolytic streptococci were not found in infants' throats and special conditions may be necessary for the colonization of these organisms. It should be noted here that Bloomfield's method of making his cultures was to streak the surface of the blood agar plate. We have found from previous experience[3] that a greater percentage of hemolytic streptococci may be demonstrated by pouring blood-agar into plates after inoculating the liquid medium.

Pilot and Tumpeer[1] in a series of 75 children varying from six weeks to ten years of age, demonstrated hemolytic streptococci in 47.7 per cent of throat cultures. However, 89.3 per cent of 28 pairs of tonsils removed from children between two and six years of age revealed hemolytic streptococci of the beta type. Hemolytic streptococci were found in the throats of two infants, each six weeks old. They concluded that the beta hemolytic streptococcus resides in the throat as well as the pneumococci, nonhemolytic streptococci of alpha type, staphylococci, diphtheroids, and gram-negative cocci, and may be dangerous secondary invaders. McCartney[9] described the bacterial flora of healthy children as consisting of only a few colonies of alpha and beta hemolytic streptococci, the viridans type of streptococci, staphylococci, pneumococci, and gram-negative cocci. The hemolytic streptococci found in normal throats were few in number.

In our observations cultures were made from the newborn of the Research and Educational Hospital. Swab cultures were made of the surface of the infants' throats in the region of the tonsils daily or every other day during the ten-day period of their residence in the hospital. The infants were placed at the mothers' breasts after the eighth hour of life and every eight hours thereafter, until the third day when they were nursed every four hours. Insufficient breast feedings were supplemented by formula feedings of certified cows' milk diluted with water and boiled for ten minutes. After cooling, nonsterile dextrimaltose was added. The possible sources of contamination were the mother, attendants, and the supplemental feeding, which at times contained Bacillus coli.

The swabs were placed in sterile tubes and taken immediately to the laboratory; to each tube was added 2 c.c. of sterile saline solution and allowed to stand for twenty minutes at room temperature. Inoculations were made by dipping the swab quickly into melted ascitic blood agar. The medium[10] was made by adding to meat infusion agar (2 per cent) P_H 7.6, defibrinated human blood and ascitic fluid in proportions of 0.5 c.c. of blood, and 2 c.c. of ascitic fluid to 10 c.c. of agar. Second dilutions were not necessary. When only two loopfuls of the saline were employed, usually no growth was obtained.

The plates were examined primarily for hemolytic streptococci with wide zones. We used the classification followed by Brown[3] who differentiated as the beta type, hemolytic streptococci with wide zones from the less hemolytic alpha type.

Cultures were made from 32 infants' throats within the first twenty-four hours. Ten of these presented growths on the first culture. (Table I.) Cultures from Babies 18 and 93 were taken before nursing and revealed a slight growth. No streptococci were present however.

TABLE I

BABY NUMBER	AGE	FLORA
93	2 hours	Slight growth—no streptococci
18	5 hours	Slight growth—no streptococci
107	11 hours	B. coli, staphylococcus
28	12 hours	Hemolytic streptococcus (beta)
110	12 hours	B. coli, green streptococcus
112	18 hours	B. coli
70	20 hours	Green streptococcus
69	24 hours	Green streptococcus
91	24 hours	Green streptococcus
106	34 hours	Green and alpha streptococcus

Ten of the 24 cultures taken for the first time during the second twenty-four hours of life contained bacteria. Seven yielded green streptococci, 2 Bacillus coli, and 1 contained alpha type of hemolytic streptococcus.

Of cultures taken from 56 infants during the first forty-eight hours of life, 36 remained sterile, while 29 contained organisms. Of 22 cultures taken for the first time during the third twenty-four hours of life, 2 were sterile but cultures from these infants on the following day contained organisms. All the cultures taken within the first seventy-two hours contained green streptococci, except those from 2 infants which yielded streptococci of alpha type, and 1 which revealed staphylococci. Cultures from 87 of the infants yielded Streptococcus viridans on one or more occasions. Some infants left the hospital before repeated cultures were obtained. The infants' throats were usually sterile for the first eleven hours, after which interval, the mouth cavity became invaded by microorganisms. The majority, 66 per cent, of infants' throats remained sterile for the first forty-eight hours. After seventy-two hours, all the infants' throats contained some organisms.

The most constant organism found was the Streptococcus viridans. This organism was found in repeated cultures in predominating numbers and even in pure cultures. B. coli was recovered in several throats when infants were a few days old but rapidly disappeared in successive cultures. The supplemental milk feeding often contained B. coli when this organism was found in the throat. B. coli did not adapt itself to the mucous membranes of the throat for a long period and only one infant yielded B. coli on the twenty-third day. However, B. coli was found in 3 infants before feeding. This may be due to contamination in the birth canal, especially in labor of long duration. Staphylococcus albus was found frequently and varied in successive cultures from hemolytic to nonhemolytic types. Little attention was paid to the gram-negative organisms except for recognizing their presence in many of the plates.

Colonies with clear hemolytic zones, varying from 1 to 2 mm., were more frequent than the typical beta hemolytic streptococci, but were found less frequently than the Streptococcus viridans. None resembled Streptococcus epidemicus. The alpha hemolytic streptococci comprised a small number of the colonies on the plate. Twenty-nine infants' throats in the series revealed this organism at some time during the ten-day period. Hemolytic strains giving narrow and wide zones were tested for hemolysis by mixing 0.5 c.c. of a twenty-four-hour broth culture and 0.5 c.c. of a 5 per cent solution of washed human red blood corpuscles. The suspension was incubated for two hours, read, placed in the refrigerator overnight, and read again. Four of the 17 strains tested, completely hemolyzed the red blood cells and were considered to be typically the beta type. The other 13 strains were incompletely hemolyzed. The narrow zone colonies, with partial hemolysis, were then classed as alpha type. The 4 strains from Babies 19, 28, 68, and 70, with complete hemolysis, continued to grow with wide hemolytic zones. In broth cultures obtained from Babies 19 and 28 a flocculent growth appeared, from Baby 68 a homogeneous growth, and from Baby 70 a granular growth. Dextrose, maltose, salicin, and lactose were fermented, but inulin, mannite and raffinose were unchanged.

Five-tenths c.c. of the twenty-four-hour culture was injected intraperitoneally into mice. The mice injected from organisms from Babies 68 and 70 died promptly in eighteen hours. The mouse injected with strain from Baby 28 died in forty-eight hours. Culture made from heart's blood of this mouse resembled Streptococcus epidemicus. The mouse injected with strain from Baby 19 did not die within forty-eight hours.

The babies in whom the hemolytic streptococci of beta type were found exhibited no unusual symptoms or elevation of temperature. The streptococcus appeared on the ninth day in Baby 19. In Baby 28 the organism was found after the twelfth hour and was not seen again in the five succeeding cultures. In Baby 28, the streptococcus appeared in two successive cultures on the ninth and eleventh days. In Baby 70 the organism was demonstrated on the fifth day and was not seen again in the two following cultures.

The beta hemolytic streptococci, therefore, were infrequent during the first ten days of life in swab culture. When present, there were but few colonies. Beta hemolytic streptococci apparently were not a part of the habitual surface flora of the throat. However, this does not rule out the presence of hemolytic streptococci in the crypts of the tonsils.

Cultures were taken of Baby 80 at intervals up to forty days and the same bacterial flora was exhibited on the last day as was present on the twelfth day. Baby 61 was seen in the dispensary six weeks after leaving the hospital and the same flora was present as was noticed on the third day of life.

SUMMARY

Three hundred and eighty-seven throat cultures from 130 newborn infants were taken. Ten of 32 cultures taken during the first twenty-four hours and 20 of 56 cultures taken during the second twenty-four hours of life contained colonies of green streptococci, B. coli, and staphylococci.

Seventy-eight cultures taken within the first seventy-two hours of life contained organisms. Two infants' throats remained sterile but showed organisms on the following day.

Four beta type of hemolytic streptococci were found in this series, but were not present constantly.

Twenty-nine infants contained alpha type of hemolytic streptococci in

repeated cultures. Green streptococci were the most common invaders and were present most constantly.

Beta hemolytic streptococci were found rarely on the surface of infants' tonsils as compared with their frequent appearance in children and adults.

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185 NORTH WABASH AVENUE

REPORT OF A CASE OF SYMPUS APUS, A RARE FETAL ANOMALY*

BY RALPH A. REIS, M.D., AND JOSEPH L. BAER, M.D., CHICAGO, ILL.

CONGENITAL sympody is an unusual type of fetal anomaly produced by varying degrees of fusion of the lower extremities. Such a fusion presents the appearance of a fish tail and the fetus therefore resembles the mythical mermaid. This resemblance has given rise to the name "sirenomelus" or mermaid foot.

Mrs. L., a twenty-three-year-old housewife was referred by Dr. Phil A. Daly under whose care she had been for the past five years for late congenital syphilis complicated by a true lipoid nephrosis. Her pregnancy was uneventful until the thirtieth week when spontaneous labor set in. Effacement and dilatation were complete in three hours and the delivery was spontaneous and uneventful. The fetus was still-born.

Gross Description of Fetus.—The fetus measured 30.5 cm. in length. The head was dolichocephalic in type. The region of the genitalia was completely covered by integument and no external genitalia were present. The anal region was also covered by an external integument and no anal opening was present. The lower extremities were represented by one limb which was double the diameter of an extremity which would correspond to the size and age of the fetus. This extremity was 10 cm. in length and terminated sharply, the end being formed by one toe, the nail of which was clearly demonstrable. In the region of the anus there was a reduplication of skin assuming the form of a small tail and measuring 0.5 cm. in length.

The subcutaneous tissue of the skull showed a large amount of partly liquid and partly clotted blood. The brain showed no abnormalities. The subarachnoid space contained a moderate amount of a reddish viscid material. The subarachnoid vessels were hyperemic.

The subcutaneous tissues of the chest contained a moderate amount of clotted blood. The lungs were atelectatic and did not float. The heart and lungs showed no congenital anomalies. The liver and spleen were normal. In place of the kidneys which were absent, two large adrenals were found which were brownish in color and measured 10 by 13 mm. in diameter. In the region of the urinary bladder there was a large cyst 15 mm. in diameter. On either side of this cyst were two other cystic masses, 18 mm. in diameter. These laterally placed cystic masses were subdivided

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into many smaller cystic masses and were, apparently, remnants of kidney structure. They were attached to the vesicle in the midline by means of small thin cords. The urethra was absent.

Both ovaries were found in the midline posterior to the large vesicle which apparently was the urinary bladder. The ovaries measured 8 mm. in length. A tube could be made out lateral to either ovary. Each tube ended in a blunt button-like thickening which was blind. The uterus and vagina were absent.

The large and small intestines were not attached to the posterior wall of the abdomen. The large intestines showed a free mesentery. The esophagus and stomach

Fig. 1.—Sympus apus. Anterior view.

showed no abnormalities. The distal portion of the sigmoid was distended, measured 1.5 cm. in diameter, and ended blindly in the pelvic region. In the region of the rectum, there was a small tubelike structure which was attached to the perineal tissue and which ended blindly in the abdominal cavity.

The aorta and its branches showed no abnormalities.

There was a marked scoliosis of the lumbar vertebrae. The sacrum was horizontally placed. The pubic bones were attached to each other and showed no rami. The obturator foramina were easily recognizable. Both femurs could be made out. They were fused in most of their course and the condyli were also fused. Neither the tibia nor fibula of either side was recognizable. There was one os tarsum and three ossa metatarsalia present, corresponding to the one toe.

Diagnosis.—Sympus apus, atresia of anus and rectum, agnesia of the uterus and vagina and congenital anomalies of the kidneys.
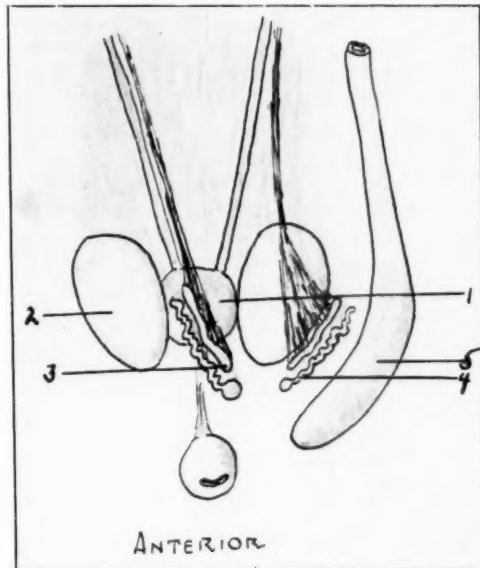
Fig. 2.—Sympus apus. Sketch of pelvic organs. *1*, Urinary bladder; *2*, cystic kidney; *3*, ovary; *4*, fallopian tube; *5*, sigmoid ending in blind pouch.

Fig. 3.—Sympus apus. Roentgenogram. Note the pelvic anomalies, the fused femurs and the absence of both tibiae and fibulae, the tarsal bones and the metatarsal bones of four toes.

Comment.—There are three distinct types of congenital sympody described in the literature. Sympus diapus shows a fusion of the lower extremities due to a fusion of the soft tissues but with two distinct and separate feet. Sympus monopus shows a complete fusion, including the feet but with two distinct sets of the bones of the lower extremities. The third type, sympus apus, has in addition to the complete fusion of the lower extremities, a congenital absence of both feet. All the types of sympody show characteristic malformations of the pelvic bones and lower spine. The specimen here reported fits the description of this third type and must therefore be classified as a sympus apus. It has in addition to the sympody a horizontally placed sacrum and the typical malformations of the pelvic bones.

Birnbaum, Schwalbe, Lenz, Lange, Bauereisen and Ballantyne have all reported cases of sympody but every case found in the literature showed two complete sets of bones of the lower extremities. This case seems to be unique in that the femurs were united and practically all the other bones of the lower extremities were missing.

104 SOUTH MICHIGAN AVENUE

A PRELIMINARY REPORT ON THE USE OF SODIUM AMYTAL AND SCOPOLAMINE ANESTHESIA DURING LABOR

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THE various methods of inducing analgesia and amnesia during labor in present use at the Boston Lying-in Hospital are by means of pantopon and scopolamine and either continuous or intermittent gas-oxygen. Pantopon and scopolamine are used only in primiparae and are fairly satisfactory, but they do not produce complete amnesia in the majority of cases and have the disadvantage of occasionally affecting the baby if given late. Gas-oxygen used in primiparae and multiparae is extremely expensive and requires the constant attention of a trained anesthetist or of a physician. In an effort to eliminate the disadvantages of the present methods and at the same time to retain their advantages a study was instituted of sodium amytal and scopolamine in one hundred unselected cases.

We have used sodium amytal in capsules given by mouth and found it to be an excellent sedative, both in cases which require rest and sleep and as a preoperative measure. Used alone during labor, however, it does not produce amnesia. Our patients remembered pains although they rested and slept during the interval. Sodium amytal alone given by mouth is not as effective as pantopon and scopolamine. We have used sodium amytal intravenously in a few cases and found it to be unsatisfactory, since the patients all became very irrational and impossible to manage. In the effort to produce complete amnesia, we decided to combine scopolamine, given subcutaneously, with sodium amytal, given by mouth.

A standard initial dose of sodium amytal, gr. ix, followed in half an hour by scopolamine, gr. 1/100, for a patient weighing one hundred and

thirty pounds was agreed upon and was considered safe for a person of this size. For a patient weighing less we have tried sodium amytal, gr. vi, as the initial dose, and for those weighing over one hundred and ninety pounds we have given sodium amytal, gr. xii. Our series included 51 primiparae and 49 multiparae and the method worked equally well in both types of cases, provided medication was started early enough in labor.

The average duration of labor for multiparae was less than five hours; for primiparae less than ten hours. In this series of 100 cases, medication was started when the dilatation in 45 patients was one and one-half fingers; in 29 patients, one and one-half to two fingers, and in 26 patients, two and one-half fingers or more. We have found that patients who are delivered in less than two hours from the time of the first medication are less likely to have amnesia than those treated early; whereas the patients seen early in labor and treated immediately had excellent amnesia, although in some cases it was necessary to repeat the medication.

The standard initial dose was given to 51 patients. An additional dose of sodium amytal, gr. iii, and scopolamine, gr. 1/150, was given to 29 patients who were in labor over three hours. The medication was given when the patient seemed too rational for a perfect end-result. This conclusion was arrived at with difficulty, because some of our patients seemed quite rational and yet had complete amnesia. One of our patients, a multipara, in labor 15 hours, seemed resistant to the medication and the initial dose was followed in three hours by sodium amytal, gr. vi, and scopolamine, gr. 1/150, which was repeated in about three hours. There was no ill effect noted with this dosage to either the mother or the infant. In 6 patients, each weighing less than one hundred and twenty pounds, sodium amytal, gr. vi, and scopolamine, gr. 1/100, did not, according to our observations, give as satisfactory effect as when a standard initial dose was given.

Not all of these cases were normal. In the series there were several patients with rheumatic heart disease and mitral stenosis, a few women had tuberculosis, and in some instances stimulation with pituitary extract was necessary. One of the tuberculous patients had a breech extraction without general anesthesia and had complete amnesia. On another tuberculous patient a dilatation and curettage was performed without any general anesthestic and with equally good results. We feel that our results are very gratifying, since most of our patients state that they remember absolutely nothing.

In classifying our results, we counted those who had complete loss of memory from the time of medication 100 per cent effect; those who seemed to us to have been irrational during labor yet who said their memory of labor was vague and that they remembered slightly some of their pains, 75 per cent (fair result); those who remembered more than this latter group we considered failures.

Eighty-four of the patients in this series fall into the 100 per cent

group; 10 of the patients fall in the 75 per cent group; and 6 fall in the failure group. We believe it only fair to say that the 10 patients in the 75 per cent group had results as satisfactory as those we are accustomed to seeing with the use of pantopon and scopolamine. As was mentioned above, of the 6 failures, 4 were given medication when the cervix was fairly well taken up, were soon in the second stage of labor, and were delivered before two hours had elapsed. The remaining two failures were primiparae delivered in less than three hours. We believe it is justifiable to say that these last 6 cases were too far advanced in labor for perfect results to be expected, and should have had gas-oxygen. Several similar patients however, who were delivered in less than three hours, had complete amnesia. Some patients seemed to be definitely more susceptible to sodium amytal than others, and this may also account for some of the differences.

In comparing pantopon and scopolamine with sodium amytal and scopolamine the determination of the exact condition of the cervix is essential for a perfect end-result in either case. Pantopon and scopolamine when given early may stop labor; sodium amytal will not. Pantopon and scopolamine when given late may produce a sluggish baby; sodium amytal will not. Pantopon and scopolamine are used chiefly for primiparae, less often for multiparae; sodium amytal and scopolamine may be used equally well for both. Pantopon and scopolamine, in our clinic have not been as effective in producing amnesia as sodium amytal and scopolamine.

Studies of this series so far have shown that there is no appreciable fall in blood pressure, no added postpartum hemorrhage, no respiratory or cardiac effect, no effect on the babies, and the necessary amount of gas-oxygen and ether at the time of delivery is markedly reduced. Detailed studies of the above are to be given in a subsequent paper.

There is one disadvantage from the nursing standpoint; namely, a few patients become quite restless particularly during the second stage of labor and have to be watched carefully. However, this can be easily done. The less the patient is restrained, the less irritable she will be, and we have found that it is of utmost importance to impress this on the attendant. No patient who has been given this combination of drugs should ever be left unattended. In our series there were 4 patients who were definitely irrational. A few breaths of drop ether were given and the patients immediately quieted down, labor continued, and they delivered several hours later.

An advantage that has not been mentioned and yet one which seems to me extremely important is that the patients sleep several hours after delivery. They rarely awaken until several hours after they have been returned to their rooms. Primiparae, as well as multiparae, will frequently ask some six to twelve hours after delivery when they will have their

baby and are extremely surprised as well as happy that the dread ordeal is over.

Another advantage is that when desirable a patient may be given the first dose in her room. When this has become effective, she may be moved to the delivery floor for further medication and delivery, later returning to her room without knowledge of having left it.

SUMMARY

Sodium amytal and scopolamine cause complete amnesia in the majority of cases, if given early. It can be given much earlier than pantopon and scopolamine with much better results. It can be given late in labor without untoward effect but is best given early. It does not slow labor or affect the baby. This combination saves general anesthesia and is far less expensive. Patients sleep several hours after delivery.

THE VALUE OF KIDNEY VISUALIZATION IN PREGNANCY
A PRELIMINARY REPORT*

BY E. L. CORNELL, M.D., AND C. H. WARFIELD, M.D., CHICAGO, ILL.

KIDNEY and bladder complications occur often enough for the obstetrician to welcome the new drugs used to visualize the urinary tract.

Since February, 1931, on the obstetric service of the senior author at the Cook County Hospital, x-ray examinations have been made of all urinary tract complications during pregnancy and the puerperium. We have also taken films of apparently normal pregnant women. While this subject has not been thoroughly exploited, the results warrant this preliminary report.

Normal pregnant women, who have no complaints referable to the urinary system, may show a marked dilatation of the right ureter. This is many times accompanied by kinks which are located in the upper half of the ureter. From the roentgenogram, one would think that these were more than twists in the ureter. They seem to be reduplications in some instances, while in others they are more or less right-angled foldings. We have found no strictures in the ureter up to the present time, nor have we seen any evidence of stone. The left ureter shows a dilatation to a much lesser degree and only occasionally have we seen kinks. The ureter on the right side shows evidence of dilatation from the third month on.

The ureters became visualized to the level of the fifth lumbar vertebra but were seldom seen lower. All cases of hydronephrosis showed hydroureters. Two pregnant women showed displacement of the ureter by the uterus. In all cases the bladder has been saddle-shaped. This is so, re-

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gardless of whether the baby lies in a breech or cephalic presentation and is seen as early as two and a half months. It is seen in roentgenograms taken ten minutes after the injection of skiodan.

It was thought that the saddle-shaped bladder might be a diagnostic point in pregnancy but on using skiodan in a case of a large uterine fibroid, it was found that the bladder assumed an even more marked saddle-shape. One must conclude that the weight of the uterus is the cause for the shape assumed by the bladder.

Fig. 1.—Case 15692. Patient aged seventeen, para O, grav. i, L.M.P. December 13, 1930. Admitted April 22, 1931 complaining of pain in the back and right loin, chills and fever of four days' duration. Temperature 101.4° F., urine showed 4+ albumin and many pus cells. Diagnosis: right-sided pyelitis. Patient was given skiodan the next day. She had a slight chill while it was being injected. This roentgenogram was taken ten minutes after injection.

In patients with cystitis or pyelitis, we invariably found a marked kinking in one or both ureters, and also marked dilatation. Pyelograms have been made in a number of instances and those have confirmed the diagnosis made by using skiodan intravenously.

Skiodan was the drug used in all cases, 20 gm. dissolved in 50 c.c. of sterile water being the dose used. The drug is now supplied in containers ready for use. Films were exposed ten minutes, thirty minutes, one hour, and four hours after the injection. In only two patients were there any reactions. In each of these there was a complicating pyelitis with a

Fig. 2.—Case 15692. Roentgenogram taken thirty minutes after injection.

Fig. 3.—Case 15692. Roentgenogram taken an hour and a half after injection. Note the marked kinking in both ureters, the right being more pronounced than the left. There is a marked dilatation in the right ureter.

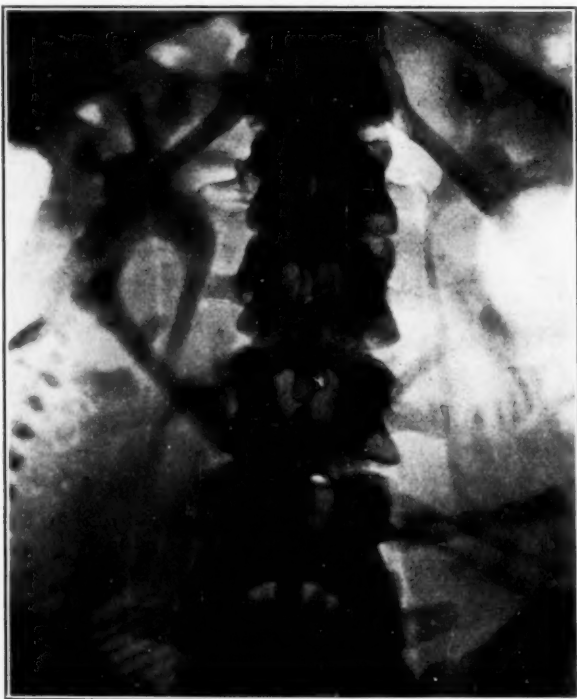Fig. 4.—Case 15692. Roentgenogram taken three hours after injection.

Fig. 5.—Case 14310. Patient aged thirty, para i, grav. ii, had a normal pregnancy of seven months' duration. She had no kidney complaints. The roentgenogram was taken three hours after the injection. Note the retention of the dye after this long period.

temperature 102° to 104° F. Each patient complained of a slight chill which lasted only a few minutes. One of these patients seemed to have a therapeutic effect from the drug, all symptoms of pain and temperature subsiding in forty-eight hours. Whether this was a coincidence is difficult to state.

The pathologic kidney is slow to visualize as compared to the normal and it retains the opaque material much longer. Good shadows of the pathologic side were seen as long as three hours after injection. Normal kidneys showed the best visualization in ten minutes after injection.

The only drawback to taking roentgenograms of the urinary tract in this manner is the inability to visualize the pelvic portion of the ureter. We have tried to show it with the urinary bladder full, partially full, and empty, but so far we have not been consistently successful. We also used the Trendelenberg position with no success.

At present the senior author feels that visualization of the urinary tract in normal pregnant women may show that accepted facts will have to be revised.

Again, it offers a means of confirming urinary tract disease diagnosis without great discomfort to the patient and at less cost. It further allows the obstetrician to decide more accurately whether or not a patient should be examined with the cystocope or catheterized. The distressing complication of hydronephrosis can be easily recognized without instrumentation.

122 S. MICHIGAN AVENUE

Vogt, E.: Fetus and Vitamin A. München. med. Wchnschr. 42: 1748, 1929.

Vogt calls attention to the importance of vitamin A in metabolism and growth, and refers to the effects of feeding young animals with a diet in which vitamin A is absent, namely, cessation of growth, loss of weight, xerophthalmia and keratomalacia. He discusses the close relationship existing between the vitamins and the endocrines.

Vogt details the results of experiments made to determine the amount of vitamin A in the various organs of the fetus during the latter half of pregnancy. Instead of using feeding experiments in this work, he utilized the color reaction devised by Rosenheim and Drummond with antimony trichloride. By means of this test on 8 fetuses varying in age from five to nine months, he found vitamin A stored in the liver only, and not present in other organs. He concludes that the liver is the chief organ for storage and metabolism of vitamins in the fetus.

A. SHULMAN.

Society Transactions

CHICAGO GYNECOLOGICAL SOCIETY

STATED MEETING, JUNE 19, 1931

Dr. Harry W. Fink reported a case of **Rupture of a Pregnant Uterus Into the Bladder**.

The specimen is from a colored woman aged thirty, who when four months pregnant fell down a flight of stairs. Two days later the hematuria, which began soon after the accident, became more marked and urination frequent and painful, accompanied by considerable distress in the lower abdomen. She was admitted to the hospital on September 23, 1928, and for a short time she seemed to improve on expectant treatment. The blood count was as follows: Red blood cells 4,850,000, white blood cells 14,600, hemoglobin 75 per cent. She belonged to Group 4. On the morning following admission she developed signs of alarming internal hemorrhage. The abdomen was not rigid but there was a mass corresponding to a gravid uterus extending to the umbilicus. It was smooth and firm. It was possible to feel a small mass slightly posterior in the fundus. The blood picture had changed so that the red blood cells were 3,500,000 and hemoglobin 60 per cent. The cervix was edematous and pale in color. The os was not open and there was no evidence of hemorrhage. X-ray showed only the presence of a mass in the abdomen corresponding to the physical findings. Several grams of bloody urine were removed by catheter. A cystoscope was then inserted and air injected. It returned around the cystoscope and a second x-ray failed to show the presence of air in the peritoneal cavity. Further distention of the bladder was not performed. The diagnosis at this time was ruptured gravid uterus associated with a dissecting hematoma, involving the posterior wall of the bladder. Because of the patient's weakened condition, the very evident shock, and progressive hemorrhage, she was a poor surgical risk. She was given a blood transfusion by the direct method but died a few hours later. An autopsy was performed and the anatomical diagnosis was as follows: Ruptured pregnant uterus into the posterior bladder wall; large hematoma of the urinary bladder (3000 gm. of blood clot); pregnancy of about four months' duration; old adhesions between the posterior bladder wall and the anterior uterine wall with marked thinning of both; adhesions between the bladder and anterior abdominal wall; and old healed midline laparotomy scar.

In reviewing the patient's past history, it was found irrelevant except as it pertained to her pregnancies and to a previous gynecologic operation about one year before her accident. She had been pregnant four times. The first two resulted in miscarriages at six weeks and four months respectively. She had been told during her second pregnancy that she had a fibroid. During her third pregnancy at three months and with a fibroid, she was operated upon. The findings were a pregnant uterus and a large fibroid the size of a grapefruit extending from the left horn of the uterus. The uterus was studded with small fibroids, varying from the size of a pea to that of a pecan nut. A myomectomy was done, the large fibroid being removed by excision and numerous small fibroids shelled out. The pregnancy was terminated and all placental tissue removed, after which the uterus was sutured and the abdomen closed in layers. The general postoperative condition was negative except for several stitch infections necessitating a stay in the hospital of twenty-seven days.

It is presumed that the trauma one year later was sufficient to produce a rupture of the pregnant uterus through one of the weakened scars in that organ.

DR. SOL LITT reported a case of **Double Uterus**.

S. T. a girl fourteen and one-half years of age, entered the Michael Reese Hospital on June 3, 1931, complaining of excessive vaginal bleeding for the past seven months. The menses began at thirteen years, were regular every 30 days and lasted five to six days for the first seven months. The last normal period was in November, 1930. Three weeks later the patient had a severe hemorrhage from the genitalia lasting three days. Since then she flowed every two weeks for six to seven days with spotting in the intervals.

The past history was not significant. Physical examination revealed a large, well developed girl appearing older than fourteen years and weighing 67.74 kilograms. General examination was negative. The introitus readily permitted vaginal examination which revealed a cystic mass 3 by 4 cm. in diameter in the anterior vaginal wall encroaching on the vaginal canal and obliterating the anterior fornix. The cervix was behind the mass. The adnexa were normal to palpation. The provisional diagnosis was congenital cyst of the vaginal wall, possibly Gärtner type.

In order to visualize the corpus uteri and appendages, a transuterine pneumoperitoneum and lipiodol instillation was performed. The interpretation of the film was unicorn uterus with right tube patent.

On June 13 an operation under spinal anesthesia was performed by Dr. Lackner. A left paravaginal incision was made, and the vaginal mucosa over the cystic mass incised and dissected away. In attempting to free the mass from the anterior wall of the cervix, the tumor was opened and about 100 c.c. of tarry black material escaped. The dissection was completed and a double uterus was found. There was no connection between the two uteri. The internal os of the left uterus was represented by a deep constriction and communicated with the sacculated hematocervix which protruded downwards and anteriorly in front of the cervix of the right uterus and formed the mass felt vaginally. The right uterus deviated sharply to the right and was connected to the vagina by the cervix. The urinary bladder was situated in the depression between the two uteri. Each uterus had a tube extending from its cornu. Two ovaries were present, each in normal relation to its tube. The left hematocervix and uterus were excised, leaving the tube and ovary. The right uterus, tube, and ovary were left in situ.

DRS. RALPH A. REIS AND JOSEPH L. BAER presented a paper entitled **Separation of the Symphysis Pubis Following Spontaneous Labor**.

DR. SAMUEL KAPLAN (by invitation) presented a paper entitled **Blood Chemistry Study in Normal Pregnancy and Eclamptogenic Toxemia**. (See page 673.)

DR. R. A. LIFVENDAHL presented a paper entitled **Modifications of the Hormone Tests for the Diagnosis of Pregnancy**. (For original article see page 721.)

DISCUSSION

DR. SYDNEY S. SCHOCHET.—We are not blind to the virtues of all these tests, but it seems to me that the gynecologists are losing sight of the fact that the clinical history and physical findings are often sufficient to make an early diagnosis of pregnancy. Chipman called attention many years ago to the softening of the uterus

and undue pulsation of the uterine vessels in very early pregnancy. This with the classical textbook findings should suffice in the making of a diagnosis of pregnancy. These tests may be essential in certain cases and play an important rôle in the diagnosis but to make it a routine procedure is not to be sanctioned. This test is exceedingly valuable in cases of chorionepithelioma.

DR. EDWARD L. CORNELL.—At the Cook County Hospital, we used the Schneider test in 14 cases of pregnancy and one of hydatid mole, 15 cases in all.

The hydatid mole gave a very strongly positive result. A week afterwards we retested the same patient and the test was still strongly positive. I made a diagnosis of chorionepithelioma which was later confirmed. I want to record two failures. One woman apparently had a three months' pregnancy complicated by a fibroid tumor. The report came back after thirty-six hours negative. I saw the ovaries and there were absolutely no hemorrhage of any character. The rabbits had received 5 c.c. of urine. On those findings the surgeon operated. He made a diagnosis of pregnancy complicated by a fibroid and closed the abdomen. The test was made last March and the patient was still pregnant at the time of reporting. The second patient had a tumor the size of a four and one-half months' pregnancy. We used the test as a routine but also checked her with the x-ray. The films showed a fetus. The test was negative in the rabbit. From these findings we decided that the rabbit test was not as accurate as it might be.

DR. P. F. SCHNEIDER.—In the use of this test it seems there is a certain unavoidable percentage of error. To avoid that and not cause serious mistakes it seems advisable to follow the suggestion of Dr. Schochet and use the clinical history and physical findings to check the test. Occasionally the source of error can be traced to the rabbit. Some rabbits have very small flat ovaries which have no visible graafian follicles. If at autopsy flat ovaries are found, it should be known that the animal is not a proper test animal and another animal should be used and the test repeated.

The test has its limitations. In a series of between 400 and 500 cases, we have had three cases in which a positive diagnosis was made before the patient had even missed a period. On the other hand, there were several cases in which a negative diagnosis was obtained five to seven days after a menstrual period had been missed. Repetition of the test several days later gave a positive result in each instance. This indicates, with some other cases in which we knew the definite date of the intercourse responsible for the pregnancy, that the reaction becomes positive about three weeks following the date of intercourse.

DR. ALFONS BACON.—After deducting our initial failures (9 cases) with the Ascheim-Zondek test and deducting 29 more for failure to submit reports because of death of the mice and inability of obtaining follow-up reports, I will report on 76 cases in which the reports were later confirmed by the patients or doctors. In cases in which the mice died, the cause was almost always to be found in cystitis or a pyelitis or the specimens had been sent through the mail and became highly toxic. Of the 76 cases, 37 or 49 per cent were positive, which were correct; 34, or 45 per cent, were negative, which were correct, and 5, or 6 per cent, were incorrect reports. Of the incorrect reports all but one were negative which should have been positive. The single exception (number 42) was in the case of a woman of forty-five who was going through the menopause and in her case only one of the four mice used showed a true positive reaction.

I have included in these figures a few special cases which I wish to mention.

Number 43 was a patient with a hydatid mole who had been curetted a few days previously and she gave an unusually strong positive reaction. This, of course, was to be expected.

Number 46 was the same patient two weeks after the curettement. It was like a normal positive reaction.

Number 55 was the same patient six weeks after operation and the result was negative. In this case we made a diagnosis of no chorionepithelioma developing.

Number 84 was another case of hydatid mole, two weeks after operation, which gave a negative reaction. In this case the same diagnosis was made.

Number 99 was a case of missed abortion done seventeen days after the initial hemorrhage, giving a negative result. The curettage following the test confirmed this result.

We also had a case (number 94) similar to the one Dr. Cornell reported, where the diagnosis of pregnancy with fibroid was made with the aid of this test. When we operated, we found this to be correct. In several cases we have had the opportunity, because of negative reports, to save patients from operations which had been planned on account of suspected pregnancies.

Another suggested application of this test is in case of sterility after performing a tubal insufflation, when, for fear of disturbing a pregnancy which may have just started, this test is applicable in helping to determine whether another insufflation may be attempted or not.

In looking over our figures, I find the majority of incorrect results to be among the first half of the cases I have just reported. From several cases we have learned that individual mice will not react true to form; hence, the advisability of using several of these test animals. I cannot see why such experiences may not occur with other test animals.

DR. SIDNEY KLEIN.—In reviewing the literature, I found but five cases reported of ectopic pregnancy with positive A-Z tests. I then reported one and Dr. Davis two; so, to date, there are eight cases with positive results.

DR. R. A. LIFVENDAHL (closing).—Whatever the method of exposure, it should be kept in mind that little manipulation of the ovary or its blood supply should be done in order not to produce artefacts.

Repeated use of the animals calls for certain precautions. If the ovary has responded with a positive reaction the animal should not be used for at least a period of three weeks. Experimentally, it has been demonstrated that the hemorrhagic bodies have an inhibitory affect upon the development of further pseudopregnancy reactions for this period of time.

Dr. Priest's suggestion of isolation of the rabbit for at least ten hours before performing the test is well taken, and I agree that this precaution should be carried out. I have used sodium amytal and chloroform but these forms of anesthesia, in my hands, have not proved as satisfactory as ether.

DR. WILLIAM A. SIMUNICH presented a paper entitled **A Comparison of the Sedimentation and Ruge Virulence Tests in 150 Gynecologic Cases**. (For original article see page 724.)

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D., ASSOCIATE EDITOR

Collective Review

A Critical Review of the Obstetric Literature of 1931

J. P. GREENHILL, M.D., CHICAGO, ILL.

A S THE title indicates the review this year is more critical and, to avoid undue length, was made less comprehensive. The outstanding papers of the year were Williams' contribution on the disappearance of the placental site, the symposium of papers presented at the White House Conference on Child Health and Protection, the symposium on resuscitation of the newborn presented before the New York Obstetrical Society, articles devoted to improvements on the original Aschheim-Zondek test, and the physiologic experiments of Ivy, Rudolph, Hartman and Koff on the uterus of dogs and monkeys.

PREGNANCY

Physiology.—In a discussion of the tetanoid syndrome in obstetrics Hartley[1] emphasizes that there are five symptoms in this syndrome namely, cramplike pains in the legs and thighs, irritability of disposition unusual in the patient, insomnia, parasthesias of the extremities and often edema of the extremities apparently not associated with cardiac or renal disturbances. The author is of the opinion that women who have menstrual cramps nearly always suffer from one or more of these symptoms in pregnancy. Richardson[2] believes that 75 per cent of all pregnant women suffer from tetany, the treatment for which is the administration of calcium best accomplished by taking viosterol. He maintains that viosterol administered during pregnancy will prevent and cure tetany, lessen the toxemias of pregnancy, improve friable perineums, prevent postpartum hemorrhage, improve the condition of the teeth, and decrease the coagulation time in the newborn. (There is no doubt that viosterol, irradiated ergosterol, is a valuable substance. Richardson is perhaps a little too enthusiastic, but all of us who prescribe this preparation know that it does help enormously women who have symptoms of tetany and also those who have trouble with their teeth. I usually prescribe thirty drops a day. In addition to taking viosterol, the patients are asked to drink a good deal of milk and eat sun-wheat cookies in order to increase the amount of calcium in their diet. If necessary, calcium gluconate is prescribed as this is probably the most pleasant and most assimilable form of calcium taken orally.)

Jarcho[3] and also Liepmann[4] discuss the value of roentgenography in obstetrics; Thoms[5] and also Walton[6] take up the question of roentgenologic pelvimetry and intrauterine cephalometry, and Kehrer[7] writes on the detection of fetal death in utero by means of x-ray. (In spite of

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the fact that roentgenography is only thirty-five years old, almost miraculous strides have been made in this field. Obstetricians were rather tardy in utilizing this valuable aid and the first extensive work in obstetrics was the atlas published by Warnekros in 1917. During the last few years roentgenography has been used extensively in obstetrics for the following purposes: (1) to make a positive diagnosis of gestation in doubtful cases in the early months, either as flat or stereoscopic plates or combined with transabdominal pneumoperitoneum; (2) to detect twins or triplets; (3) to reveal monstrosities in utero; (4) to determine the presence of an ectopic pregnancy [then combined with transabdominal pneumoperitoneum or the injection of lipiodol]; (5) to rule out pregnancy in the presence of fibroids or other tumors; (6) for the exact diagnosis of presentation and position; (7) as an aid in the study of the mechanism of labor. Not only may the first and second stages be studied but also the third stage after injecting the umbilical cord vessels with an opaque substance; (8) to study the size of the fetal head and the pelvic inlet with a view of detecting disproportion; (9) to determine the death of a fetus in utero; (10) to study the changes in the urinary tract [kidney pelvis, ureters, bladder, and urethra] during gestation; (11) to study the alterations in the symphysis pubis and sacroiliac joints; (12) to follow the changes in the position of the appendix and the base of the cecum during pregnancy, and (13) to detect abnormalities in the newborn.)

The Aschheim-Zondek test continues to be a source of study not only for obstetricians but also for a large number of laboratory investigators. Many papers on this subject were published during 1931 and among the more important ones are those by Ehrhardt[8] based upon 2,000 tests; Wiesner,[9] 835 cases; Frank, Goldberger and Felshin,[10] 321 tests; Eberson and Silverberg,[11] 175 cases; Ettinger, Smith and McHenry,[12] 137 cases; Stewart,[13] 101 cases; Finkel,[14] 52 cases; Haupstein,[15] 50 cases, and v. Ammon.[16]

Friedman and Lapham[17] suggest an improvement over the Aschheim-Zondek test which consists in the use of one unmated mature female rabbit instead of five immature mice. Their test is completed in less than forty-eight hours, whereas the Aschheim-Zondek test usually requires one hundred hours. Others who verified the superiority of the Friedman test are Davis and Walker,[18] Magath and Randall,[19] Schneider,[20] Reinhart and Scott,[21] and Wilson and Corner.[22]

Brouha and Hinglais[23] report on their test in which they use male guinea pigs instead of female ones, Mathieu and McKenzie[24] recommend the use of one female rat instead of five female mice, and Bourg[25] advocates carrying out the test using one male and one female rat at the same time. Mazer and Hoffman[26] report a comparison of the Aschheim-Zondek test, the female sex hormone test and the Siddall test. Gordon and Emmer[27] discuss the Bercovitz test for pregnancy, Kulitzky[28] studied the so-called erythrocyte sign of early pregnancy and a large number of foreign investigators reported on the Manoilov pregnancy reaction (Dierks,[29] Nerson,[30] Zelic,[31] Goldschmidt-Fürstner,[32] Luh,[33] Gymnich,[34] Moschkow[35] and Kabisch[36]). White and Severance[37] compared the following pregnancy tests: Aschheim-Zondek, Brouha, Friedman, Manoilov and Bercovitz. Sellheim[38] traces the attempts at making a diagnosis of early pregnancy from the clinical studies of Hegar through the labora-

tory tests of Abderhalden up to the results obtained by Aschheim. (The foregoing array of names, tests and modifications indicates the enormous amount of laboratory work that is being done at the present time in the attempt to make an early diagnosis of pregnancy. In spite of their relative newness the Aschheim-Zondek and the Friedman tests have definitely proved to be reliable in about 98 per cent of cases. The Bercovitz pupillary test is dependable in a much smaller percentage, whereas the Manoilov test is very unreliable in the first few months of pregnancy. The many thousands of pregnancy tests which are being performed and the innumerable animals which are being sacrificed can only be excused on the ground that the tests are relatively new and every laboratory worker wants to verify their dependability and perfect himself in their technic; for it is hard to conceive that in so many cases of normal pregnancy a diagnosis cannot be made clinically or that there is such urgency for prompt diagnosis. Early intrauterine pregnancy can still be detected in the large proportion of cases by means of bimanual examination, especially if the examination is repeated after two or three weeks. In abnormal gestations of course, these tests are invaluable. In this category belong extrauterine pregnancy, missed abortion, incomplete abortion, hydatid mole, and chorionepithelioma. When a physician is given a specimen of urine and asked to have a hormone test of pregnancy performed, he should make sure he knows the source of the urine. Likewise it is important to whom and how he communicates the result of the test.)

Abortion.—In an elaborate paper on the relationship between abortion and fetal and maternal welfare, Taussig[39] calls attention to the fact that there are approximately 700,000 abortions annually in the United States, that the number is increasing each decade and that most of the women who have abortions are married women. He believes that 15,000 women die each year as the result of abortions. The deaths from sepsis following abortion are seven times as frequent as after childbirth. In a series of 600 abortions reviewed by Hendry[40] it was found that by far the largest number were self-induced. Likewise Harbitz[41] believes that the majority of the 3,791 cases of abortion treated at the Oslo Municipal Hospital were most likely criminal in origin. In the febrile cases the death rate was ten times as high as among the afebrile cases. McConnell[42] is of the opinion that among the factors causing abortion, infections probably play the greatest rôle. According to Peller[43] there are presumably one million or more abortions annually in Germany. In large cities approximately 50 per cent of all pregnancies end in abortion but this does not mean that all the abortions are induced. According to Magid[44] there are about 400-500,000 spontaneous abortions in Russia each year. This number represents an average of 7.5 per cent of all conceptions. On the tenth anniversary of the legalization of abortion in Russia (November 20, 1930) Boyko[45] made an extensive study of abortions. Russia is the only country in the world where abortion is legalized and every woman has the right to request that it be performed if there are any indications of a social nature. The claim was made that this law would lead to a degeneration of the nation but the author disproves this assertion. In 1929 the net increase in population of Russia was 23 per thousand while in France it was only 1.3 and in England 3.4. (The above figures give an idea of the appalling number of abortions which occur throughout the world. While there has been an increase

in the incidence of spontaneous abortions, the vast majority of the early interruptions of pregnancy are induced. The exact number of the latter will most likely never be known nor will the totality of unnecessary deaths which result from it. However strongly we might condemn the Russian law concerning abortions, it certainly has resulted in a distinct decrease in the mortality following abortions; according to the law, abortions must be performed in hospitals which are, of course, far cleaner than the offices of most abortionists. Regardless of how much we try to educate women to the dangers of criminal abortion, countless numbers of them still continue to go to doctors and midwives who secretly perform abortions in unclean surroundings. The women have very little fear or at least they are willing to take a chance because they are desperate and the abortionists themselves have no regard for civil law, moral code or religion. The problem of induced [this is a better word than criminal] abortions requires further studies like that made by Taussig and conferences between physicians, law-makers, ministers, and sociologists with a view toward changing our existing laws on this matter. It is true that the proper use of contraceptive measures will reduce the number of abortions, but for many reasons this information is not being used by a large proportion of women. Furthermore, we know of no anticonceptional method which is infallible.)

Leunbach[46] and also Wolf[47] advocate the use of a paste which is inserted into the uterine cavity for the purpose of inducing abortions. (These authors and others have extolled this simple procedure which was first suggested by a druggist. However, physicians should be warned against using this paste which, because of the simplicity of its use may make it popular for producing abortions. Within a short time recently, 21 women died of embolus following the use of these pastes. Most of the deaths were due to air or fat embolism.)

Complications.—Daly and Strouse[48] discuss three important medical complications of pregnancy, namely, diabetes, heart disease and hyperthyroidism. They insist that when a woman with a medical ailment becomes pregnant, the gestation should be considered as the complication and the medical ailment the paramount issue instead of the reverse. Peckham[49] takes up the treatment of diabetes mellitus associated with pregnancy. McIlroy and Rendel[50] emphasize that efficient treatment of heart disease complicated by pregnancy depends upon early antenatal examination and the cooperation of the obstetrician and the cardiologist. (This latter point is to be especially stressed, because in every case where a medical complication is associated with pregnancy, it is important to call an internist in consultation, particularly one who has had experience in treating these complications in pregnant women. Practically every maternity hospital in this country has a staff of internists to supervise the care of obstetric patients who have medical complications.)

Mussey and Plummer[51] take up the treatment of goiter complicating pregnancy, and they analyze the results in 29 cases of exophthalmic goiter and in 12 cases of adenomatous goiter. In 22 of the 29 patients of the first group and in 9 of the 12 of the latter, partial thyroidectomy was performed during pregnancy. There were no maternal deaths during gestation or as the result of delivery. (Fortunately hyperthyroidism complicating pregnancy is very unusual. Most patients can be carried through gestation on Lugol's solution but when the thyroid intoxication becomes worse in spite of medical treatment there should be no

hesitation in advising partial thyroidectomy. There is far less danger
of interruption of pregnancy following this operation than there is if
the hyperthyroidism increased in severity. The heart must be closely
watched in all patients with hyperthyroidism. It is often wise to give
prophylactically pregnant women some form of iodine throughout ges-
tation especially those who live in goiter districts.)

Kessler[52] is of the opinion that pulmonary tuberculosis is by far
too often taken as an indication for interruption of pregnancy. He
believes that for a tuberculous gravida, sanitarium treatment is neces-
sary. Robinson[53] received 200 letters from all over the world in answer
to a questionnaire on the influence of childbearing on pulmonary tuber-
culosis. Most of the experts who answered agreed that parturition
involves a special risk for the tuberculous woman. The injurious effect
commonly begins in late pregnancy, but increases during the puerperium
and reaches its maximum when lactation has been established. On the
other hand, it is the firm belief of Blisnjanskaja[54] that the course of
pregnancy, labor and the puerperium in tuberculosis women does not
differ from that in nontuberculous individuals. From a study of the
literature Fink[55] comes to the conclusion that the teaching which favors
emptying of the uterus in every case of laryngeal tuberculosis is
fallacious. Among 360 cases reported in the literature, 75 women recov-
ered. Furthermore, only 33 recovered after interruption of gestation
as compared with 42 who were saved without any intervention. (Within
recent years most obstetricians and phthisiologists have become con-
servative in the care of pregnant tuberculous women. It is rarely
necessary to interrupt gestation for tuberculosis, and unless this is done
during the first three months, it is far safer to permit the pregnancy
to continue to term. Whenever a tuberculous patient is delivered or
operated upon and an anesthetic is necessary, local anesthesia should
be used.)

The value of the Aschheim-Zondek test in the detection of hydatidi-
form and chorionepithelioma is discussed by Nürnberger,[56] Reeb,[57]
Ginglinger,[58] Wladika,[59] Gerritzen,[60] Hady[61] and many others. (In
nearly all cases of hydatidiform mole and chorionepithelioma, there is
an unusually strong Aschheim-Zondek reaction. Thus if more than
50,000 mouse units are found, there are most likely pathologic changes
in the placenta. If 200,000 or more mouse units are present, the
diagnosis of hydatid mole or chorionepithelioma may be made with cer-
tainty. Occasionally there will be a negative Aschheim-Zondek test in
the presence of an hydatid mole as in the case recently reported by
Bleuler.[62])

Schmitz[63] advocates hysterectomy followed by radiation therapy for
cases of chorionepithelioma and Wintz[64] reports at least 8 cures out of
11 cases of chorionepitheliomas treated by roentgen ray therapy. The
latter author maintains that radium is not only superfluous but also
dangerous because of the necessary manipulation. (In recent years
excellent results have been reported in small series of cases of chorion-
epithelioma where irradiation therapy was used. Most likely the safest
procedure is hysterectomy followed by x-ray treatment. Patients who
have had hydatid moles should be closely followed for years and Asch-
heim-Zondek or Friedman tests should be performed at regular inter-
vals. In women over forty years of age, if a hydatid mole is found,
a hysterectomy should be performed because the danger of the subse-

quent development of a chorionepithelioma is far greater than in young women and the death rate is much higher.)

The Toxemias.—In the opinion of Falls,[65] Lugol's solution administered orally, intravenously or intramuscularly is of value both as a prophylactic and a curative remedy in hyperemesis gravidarium. He has not found it necessary to induce abortion for this complication since using Lugol's solution. Van Wyck[66] advocates the use of glucose solution, sedatives, attention to bowel elimination and isolation for patients who vomit excessively. The continuous administration of glucose or venoclysis is recommended by McConnell,[67] and Aburel[68] asserts he cures hyperemesis by anesthetizing the lumbo-aortic plexus. (The use of Lugol's solution as suggested by Falls will undoubtedly help many women with hyperemesis. The usual treatment consists of isolation, bedrest, subcutaneous and intravenous injections of glucose solution, sedatives, duodenal feeding in subborn cases and a good deal of psychotherapy, especially at the start. If improvement does not follow in a short time, it is best to empty the uterus.)

Nephritis in pregnancy has been the subject of a number of papers. Kellogg[69] expresses his views based upon an experience of 1,100 cases. In a group of 225 patients seen in two pregnancies, 80 per cent showed a recurrence of albuminuria and hypertension in the second pregnancy. The general impression gained from a series of 68 patients seen in more than two gestations was that with each successive pregnancy, the toxemia becomes worse earlier in pregnancy. In Schroderus'[70] series of women who had renal complications during pregnancy and who subsequently conceived again, 87 per cent had a return of the kidney disturbance. Stieglitz[71] analyzes a series of 60 cases of nephritis in pregnancy paying special attention to classification and treatment. Stander and Peckham[72] point out the bad prognosis of this complication. In their series the maternal mortality occurring within ten years was 42.5 per cent whereas the average mortality for women between thirty and forty years of age in this country is 7.5 per cent. In the presence of definite chronic nephritis, the authors advocate termination of pregnancy and prevention of further pregnancies by either contraception or sterilization. Peckham and Stout[73] reexamined a large series of women four months to four years after they had had toxemia of pregnancy excluding eclampsia and vomiting. They found that 40 per cent had a definite chronic nephritis, and they suggest that the differential diagnosis between nephritic and nonnephritic toxemia should not be made until four months after delivery. Gibberd[74] emphasizes that a previously healthy patient suffering from albuminuria during pregnancy runs the risk of developing eclampsia, patent chronic nephritis, occult nephritis, the danger of losing her baby by death in utero or by death duing the neonatal period from prematurity. (It is generally conceded that nephritis in pregnancy is a very serious complication. If the renal involvement manifests itself early in pregnancy, it is rarely possible to carry the patient along until she can give birth to a live baby. In most cases in spite of rest in bed, a strict diet and all known therapy, nothing will be gained by waiting, but a good deal of damage will result. Most of the babies perish in utero long before term, and of those which are born alive, most are puny and seldom survive. Furthermore, irreparable damage is done to the mother's kidneys with the result that her life will be considerably shortened. Hence, when a preg-

nant woman is found to have definite chronic nephritis, it is best to empty the uterus without delay unless the patient is a primipara. All the risks of waiting must be explained to the patient and her husband. Nonpregnant women with chronic nephritis should be explicitly told how to prevent conception or should be sterilized. When operating on pregnant patients who have nephritis, it is best to use local anesthesia. Women who apparently recover from nephritis, should not become pregnant for at least three years afterward and only after repeated examinations of kidney function can be considered normal. In spite of this there may be a recurrence of nephritis.)

Many articles have been written on urinary tract infections in pregnancy. McComb[75] reviews a series of cases of pyelitis, pyelonephritis and pyonephrosis occuring in pregnancy and outlines his treatment which includes ureteral catheterization. Rose and Rollins[76] wrote an elaborate paper on pyelonephritis in pregnancy and Morris and Langlois[77] describe the treatment they used in 58 cases of urinary tract infections observed during or after pregnancy. Crabtree and Prather[78] pointed out the activities of a urologist in a lying-in hospital. In their work at the Boston Lying-in Hospital, they have reversed the figures on pyelonephritis of pregnancy and postpartum pyelonephritis cases which require hospital care, they have been made cognizant of important respects in which pregnancy influences common urologic conditions in the nonpregnant, and they have had opened to them a field for conservative surgery of the kidney before renal damage has become very extensive. Crabtree[79] also discusses the changes in the urinary tract in women as the result of normal pregnancy and Prather[80] the effect of changes due to pregnancy on urinary tract disease. Dodds[81] investigated the question of bacteriuria and found that 87.2 per cent of 793 antenatal, parturient, and puerperal specimens of urine were sterile. He found colon bacilli in 5.7 per cent of the specimens and could not detect any relationship between bacteriuria and parity, period of pregnancy, septic foci, toxemia, previous renal disease or morbid puerperium. Haselhorst[82] followed up 62 patients who had pyelitis during pregnancy and found that 39 sooner or later had trouble. Thus 19 had a recurrence in a subsequent pregnancy, 3 had hypertension and 14 had edema. Grieve[83] reexamined 100 women some time after they had had pyelitis in pregnancy and found 26 who were not cured either clinically or bacteriologically, 14 who were not cured bacteriologically and 5 recurrences in 11 subsequent pregnancies. (Just as every maternity hospital has one or more internists on its staff so will every progressive lying-in hospital soon have a urologist associated with it. Urinary tract infections during pregnancy and the puerperium are very common and few obstetricians possess the necessary knowledge and skill to properly perform ureteral catheterizations and, where necessary, surgery on the kidneys. Furthermore all patients who have urinary tract infections during pregnancy or the early puerperium must be followed up and oftentimes treated for months and years afterwards and this is really the province of the urologist. Only by the cooperation of obstetrician and urologist can the best results be obtained in these cases. To neglect the follow-up of a patient who has had pyelitis in pregnancy is serious negligence, because even though a woman may apparently recover from pyelitis completely, subsequent examination in many such cases will reveal a persistence or a recurrence of the trouble. During the puerperium, a diagnosis of pyelitis is frequently made either because the

real cause of fever cannot be found or because the physician desires to cover up puerperal infection. At least one catheterized specimen of urine should be examined before a diagnosis of pyelitis is made.)

Guthmann and Ehrhardt[84] and also Gremme[85] studied ureteral dilatation during pregnancy after the intravenous administration of dyes. These authors agree that dilatation of the ureters may be found in the second half of gestation in nearly all women and is a physiologic occurrence. (This is an almost universal opinion at the present time. In most cases there are no abnormal symptoms referable to the dilatation. The latter is due to hypotonicity of the ureters. Likewise from the fifth month onward, the lower part of the abdominal ureter in pushed aside by the growing uterus and this may be found in at least 80 per cent of women after the seventh month. In many cases ureteral kinks are present. There does not seem to be any relationship between dilatation of the ureters and pyelitis.)

Eclampsia properly continues to hold the attention of obstetricians. Harding and Van Wyck[86] reemphasize their belief that the commonly occurring dietetic factor which enters into the production of eclampsia and preeclampsia is sodium chloride. Therefore restriction of salt is important during pregnancy and especially when patients have toxemia. On the other hand these authors believe that proteins and fats are innocuous to patients with preeclampsia and eclampsia. McCord[87] outlines the conservative treatment of this disease for the general practitioner. Beck's[88] study of 97 cases proved to him that phlebotomy is a very valuable measure, that eclamptic patients have a remarkable tolerance for morphine and that conservative gives far better results for the mothers than radical therapy. Schumann[89] reports 111 cases of toxemia with a death rate of 5.4 per cent. Of the 28 women with eclampsia 21.5 per cent died. The treatment was essentially conservative. Gordon[90] is likewise in favor of conservatism although he prefers emptying the uterus especially by cesarean section for patients with preeclampsia. Müller[91] is of the opinion that under similar conditions the purely active treatment yields the same results as the modified active therapy. Dieckmann[92] suggests the use of 500 to 1000 c.c. of a 6 per cent gum acacia solution in the treatment of eclampsia because there is a marked concentration of the blood. The results with this therapy have been strikingly good. Goecke[93] advocates the use of pernocton, but in spite of this he favors emptying the uterus as early as possible, especially by cesarean section. Schey[94] administers thymophysin to hasten labor in eclamptic patients and he combines this with the Stroganoff treatment. (The generally accepted treatment at the present time for the vast majority of eclamptic patients is ultraconservatism with dependence upon morphine, sedatives, glucose and perhaps laxatives. Gum acacia is certainly worthy of trial. Colonic irrigations, gastric lavage and hot packs are not only unnecessary but they may result in harm. The pregnant uterus should be left alone, unless spontaneous labor sets in during an attack, as it frequently does. In this case, labor should be shortened by eliminating the second stage if it can be done without harm. If an anesthetic is necessary local anesthesia should be used whenever possible. More important than the treatment of eclampsia is its prevention. Authorities agree that nearly all cases of eclampsia may be eliminated by proper prenatal care. While great progress has been made along these lines, about 5,000 women still lose their lives in this country needlessly each year from eclampsia. Fur-

thermore, of the 20,000 or more women who develop eclampsia each year and recover, a large proportion have some sequelae as the result of their attack.)

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PITUITRIN IN GYNECOLOGY

To the Editor: During the last twenty years the action of pituitrin in obstetric practice has been so carefully studied that its uses and dangers are well known. Pituitrin contracts smooth muscle fibers and this is especially manifest on the pregnant uterus, because of the enormous hypertrophy of the muscle fibers. It raises the blood pressure because it contracts the smooth muscle fibers of the blood vessels, and it lowers the pulse because of a like result on the coronary vessels. In consequence of this effect on the hypertrophied smooth muscle fibers of the breast, Ott and Scott, and Schäfer and Mackenzie noting the increased rapidity of flow of milk from the breast, erroneously thought that pituitrin was a galactagogue. It also for the same reason stimulates intestinal peristalsis and is therefore a valuable aid in overcoming postoperative distention of the intestines.

Though the hemostatic action of pituitrin is most outspoken in the pregnant uterus, it may be used with remarkable results in controlling the bleeding in gynecologic operative work. I have used it this way in all types of gynecologic operations now for several years in many hundreds of cases.

The danger of inadvertently perforating the uterus during curettage is well known. A hypodermic injection of 1 c.c. of surgical pituitrin into the paracervical tissues just before starting the dilatation of the cervix causes the uterus to contract and reduces this danger to a minimum. Plastic operations on the vagina are frequently so bloody and the field so obscured that none but the operator himself is cognizant of the steps in the operative technic. Pituitrin will so reduce this useless and frequently dangerous loss of blood that the steps of a difficult vaginal technic will be as readily understandable to a bystander as the processes of an abdominal operation. Used preliminary to a vaginal hysterectomy it may allow this operation to be performed even by morcellation with little danger in the anemic individual when some less indicated procedure might otherwise be felt advisable. A large fibroid of the uterus with enormously dilated vessels may contain several ounces of blood of great value to the patient if the blood could be removed from the tumor. An injection of pituitrin directly into the tumor will cause the tumor to contract and whiten and will drive out much of this valuable blood from the tumor into patient's circulation. Extensive operations which otherwise might be dangerously bloody are performed frequently with as little blood loss as one or two ounces.

Moving pictures of operations are frequently seriously obscured by the constant flow of blood. Dr. Harold Jones of St. Luke's Hospital, Chicago, recently exhibited several films made of operations under the effect of pituitrin and bleeding was so much under control that one might think that the operations were being performed upon cadavers.

One or 2 c.c. of surgical pituitrin is given into the uterine body during abdominal operations or into the paracervical tissues during vaginal work. If given into an accessible area it may be administered at the exact time desired. The effect is not a local one. Within two minutes, usually, the tissues will become blanched and the hemostasis is in action and persists for an average of twenty minutes. If necessary the medication may be repeated. At the height of the activity the anesthetist may notice blanching of the patient's face. The conscious patient at

this time may feel "queer." Blood pressure readings were taken during the course of all operations and a study of several hundred readings reveals only an occasional elevation of blood pressure to a maximum of twenty points and those only among such as had normal or low blood pressures previous to operation. At first the medication was omitted in those with elevated blood pressures. It was found, however, that the administration of the anesthetic produces a lowering of the blood pressure in such cases so latterly pituitrin has been used when hemostasis seemed desirable even when the blood pressure was quite high, and its use has never increased the pressures to a level higher than it was before the anesthetic was started.

It, of course, is imperative that strategic ligations be made as carefully when pituitrin is used as when operating without a hemostatic. If this is done I am certain that the idea that pituitrin leads to late secondary bleeding will be found in error and the supposed secondary bleeding is nothing but the escape of blood which accumulated after the pituitrin had ceased to act.

I would suggest the employment of pituitrin as a valuable agent in controlling the waste of blood during (gynecologic) operations, for I have found that it is followed by no untoward effect in a very extensive use over a period of several years.

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Dr. Charles L. Bonifield

Dr. Charles L. Bonifield, a member of the Advisory Editorial Board of this Journal, died in Cincinnati, on April 23, in the sixty-ninth year of his age. A more extended obituary will be published in the June issue.